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The
MEDICAL CLINICS
of
NORTH AMERICA

CHICAGO NUMBER

PHILADELPHIA AND LONDON

W. B. SAUNDERS COMPANY

1948

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PRESS OF
W. B. SAUNDERS COMPANY
WASHINGTON SQUARE
PHILADELPHIA

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THE MEDICAL CLINICS
of
NORTH AMERICA

CHICAGO NUMBER

FOREWORD

I am very grateful to the authors who have contributed to this number of the *Medical Clinics of North America.* In selecting subjects, special attention has been paid to the needs of the general practitioner. Each author has done outstanding work in the field which his paper covers. Of the twenty-two papers, fourteen are from Chicago, and eight from various other parts of the United States and Canada.

This volume includes a symposium on recent developments in endocrinology. Our knowledge of glands of internal secretion has increased very rapidly in the last few years. Accurate diagnostic methods have been developed and specific therapeutic agents are now available with which it is possible literally to produce modern miracles.

I believe that this volume will prove of value to those who read it.

WILLARD O. THOMPSON, M.D.
Consulting Editor

SYMPOSIUM ON ENDOCRINOLOGY

TREATMENT OF GRAVES' DISEASE WITH RADIOACTIVE IODINE

MAYO H. SOLEY, M.D.* AND EARL R. MILLER, M.D.†

THE first thyrotoxic patients to receive radioactive iodine as a therapeutic agent were treated by Hertz in the spring of 1941. Coincidentally, Hamilton, Soley and Eichorn used radioiodine (I^{131}) in rabbits and dogs in order to determine the effect in animals of single doses in amounts up to approximately thirty times the expected single dose in man. On October 12, 1941, Hamilton and Soley treated their first patients with Graves' disease with this agent. The original work of both groups was reported in abstract form in September, 1942.[1, 2] The first full reports of the therapeutic effects of radioactive iodine were those of Hertz and Roberts[3] and Chapman and Evans[4] in 1946. During the past few years, groups at the Massachusetts General Hospital, the University of California Hospital, the Presbyterian Hospital in New York, the Mayo Clinic and the Cedars of Lebanon Hospital in Los Angeles have, among others, treated an increasing number of patients. The experience of these groups is now reaching a state that permits publication of results so that I^{131} may be accorded its rightful place in the therapy of Graves' disease. Means[5] may be quoted as our guide in evaluating radioiodine: "The proof of the pudding is the eating, and similarly the proof of the treatment of any disease lies in the practice thereof, and that for a sufficient length of time and under adequately controlled circumstances. Forms of therapy ultimately survive or disappear in accordance with the impression they make on dispassionate, yet qualified observers. Time is a requisite in their appraisal."

ANIMAL EXPERIMENTS

Single doses of 300 microcuries of carrier-free radioiodine (I^{131}) obtained from the Berkeley cyclotron were injected subcutaneously in

From the Divisions of Medicine and Radiology of the University of California Medical School and the Thyroid Clinic of the University of California Hospital, San Francisco. Grateful acknowledgement is made to Miss Jean Hitch for her help in coordinating this study and compiling data.

Supported in part by a grant from the American Medical Association Therapeutic Research grant.

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rabbits and dogs. In the rabbits, the thyroid gland showed extensive necrosis, hemorrhage, polymorphonuclear infiltration and changes in all the layers of the arteries by the tenth day. At twenty days, the thyroids still showed healing vascular changes, some polymorphonuclear, lymphocytic and eosinophilic infiltration, as well as fibrosis. After thirty and forty days, further fibrosis occurred, the thyroids decreased to approximately half the expected normal weight and size, the cellular infiltration was of lesser degree and the arteries showed intimal and medial fibrosis and thickening and perivascular fibrosis; only a few acini remained at the poles and these also did not appear to be entirely normal. One dog sacrificed at forty days had a thyroid showing changes similar to those seen in the rabbits' thyroids at forty days and a single dog sacrificed at 100 days showed almost complete destruction of the thyroid and partial or complete occlusion of the arteries and veins. One rabbit showed damage to the renal tubules; glands of internal secretion, trachea, bone marrow, liver, spleen, lymph nodes, kidneys and peripheral blood counts were within normal limits on pathologic examination (Hamilton, Soley, and Eichorn[6]—unpublished data). Metabolic rates were not obtained on these animals, and their clinical condition at least did not suggest the severe thyroid deficiency that one might expect from the appearance of their thyroids.

In the past year, Miller, Lindsay and Soley[7] gave larger doses of I^{131} to animals orally to determine the effect of radioactivity on the kidneys and other organs. Rabbits were given 0.5 millicuries of I^{131} per pound orally. This was done to destroy the thyroid partially so that it would not take up too much of a large dose of iodine and produce local necrosis of surrounding tissues. Five days after this dose, animals were given by mouth up to 4 millicuries of I^{131} per pound. The animals were sacrificed at the end of four weeks. The thyroids were partly or completely destroyed at this time; in addition, there was some injury to the trachea and renal tubules. No other demonstrable damage was noted. Blood counts were not done in this group of animals.

TECHNIC

Carrier-free radioiodine calibrated in millicuries per cubic centimeter is received from Oak Ridge. We have accepted this calibration in our work. A number of attempts have been made to check this calibration and in the future well standardized solutions will be used throughout the entire country.

When the stock of I^{131} arrives, known amounts from 10 microcuries to 2000 microcuries are put into standard rubber-capped 30 cc. serum bottles, and the bottles are filled with water. These bottles are used to obtain standardization curves of millicuries versus counts per minute on the Geiger counter. These bottles are about the size and weight of a slightly enlarged thyroid.

A bell-shaped Scott-Geiger-Müller tube 2½ inches in diameter is

used. It is mounted in a lead cylinder with 1 inch walls. For standards from about 100 to 2000 microcuries a distance of 53 cm. from the bottle to the face of the Geiger tube is used. The radiation is filtered through 2 mm. of lead. Small amounts (10 to 100 microcuries) are measured at 18 cm. without a filter.

On all measurements a background reading on the counter is taken. The second measurement is the response of the counter to a 0.6 mg. radium needle which is in a lead container with half inch walls. This has acted as our arbitrary gamma ray standardization throughout the entire work. Then each of the bottles in turn is placed on a wooden phantom which resembles the neck in size, and the counts from the various standard bottles are taken. Curves are drawn using counts per minute against microcuries under the above conditions.

The patient receives the radioiodine, usually at the start of the day. The iodine solution is put in about 50 cc. of water which the patient drinks. The patient returns for the measurement of the thyroid uptake usually twice the first day, three times the second day, and once the third day. All of the urine is collected over the forty-eight hour period. It is divided into four twelve-hour specimens. The amount of I^{131} in each of these specimens is determined.

When the patient returns for measurement, he lies flat on a table and the Geiger counter is moved directly over the neck at a distance of 53 cm. from the front of the neck. A count is taken in this position. The Geiger counter is then moved over the thigh, just above the knee, again at 53 cm. The count here is taken. It will be observed that the thigh above the knee is about the same size and shape as the neck. The essential difference between the areas is the presence of the thyroid. We subtract the count from the thigh (which acts as a neck background) from the counts which are obtained from the neck plus the thyroid. This leaves the number of counts presumably due to the thyroid. In each of these measurements, background, radium counts and a standard bottle which gives us approximately the same number of counts as the neck and thyroid give, are checked. From this data one can then refer to the previous calibration curves and determine the amount of I^{131} in the thyroid in microcuries of I^{131}.

A standard 33 cc. serum bottle such as was used for the original standardization is filled with the urine from one of the twelve hour specimens. This is usually counted at 18 cm. without filter. The counts from this are then referred to a standard curve which tells us the amount of I^{131} in 33 cc. of urine. This also tells us the amount of I^{131} per cubic centimeter of urine which, multiplied by the number of cubic centimeters of urine collected in the twelve hours, gives the total twelve hour urinary excretion of the iodine.

During the course of study of the uptake of radioiodine in the thyroids of patients with various types of thyroid disease and in normals, it has been found that, in general, the uptake of radioiodine in nor-

mals is less than 30 per cent; usually it is much less than this. In patients with frank untreated Graves' disease, the uptake of iodine usually lies between 40 and 80 per cent. These observations actually have been of diagnostic significance in patients in whom anxiety states made determinations of the basic metabolic rate difficult. When the uptake of a tracer dose of I^{131} (100 to 250 microcuries) is high, the diagnosis of hyperthyroidism is usually confirmed; if it is low, the diagnosis of hyperthyroidism is not tenable.

In this entire study, carrier-free I^{131} has been used. There is no inert iodine in carrier-free I^{131}. The number of iodine molecules is so small in our dose range of I^{131} that no effect due to iodine per se is expected.

DANGERS

All radioactive material is dangerous. It must be handled with great care and should be handled by remote control instruments. The main supply of iodine is kept in a lead cylinder with thick walls surrounded by lead bricks. The following apparatus is used when transferring solutions from one container to another. A pipette is held vertically on a ring stand. A pipe runs from the top of the pipette at right angles for a distance of about 2 feet along a horizontal rod. A syringe is put on the other end of the copper pipe. When the piston of the syringe is pulled back, the fluid will rise in the pipette; when it is pushed in, the solution is delivered from the pipette. The amounts can be measured exactly. Long tongs are used to handle iodine containers. All stock solutions are kept behind lead brick. It is important, obviously, that none of the material be spilled. If the material is spilled, it should not be ingested, should not touch the skin, nor should the vapors be inhaled. It is important to do measurements of gamma ray activity around the area where the stock bottles are kept so that personnel in this vicinity are not overirradiated.

CLINICAL MATERIAL

Patients reported in this study were chosen for treatment by members of the Thyroid Committee of the University of California Hospital. All patients had undoubted Graves' disease varying from mild to severe degree, as evidenced by clinical appraisal and laboratory tests. No patients with nodular goiters were included in this series since we believe that operative removal is the treatment of choice when nodules can be palpated in the thyroid. This group of patients is a segment of a large number that are being studied under the auspices of the Atomic Energy Commission in order to determine the action of radioiodine on patients.

The uptake of radioiodine in the thyroid and its excretion in the urine were determined in nearly all the patients. The clinical aspects of the study were carried out by members of the Thyroid Committee.

Early in the course of this program, small (as little as 250 micro-

curies) and frequent (once weekly) doses of I^{131} were administered. Later, and this is true for most of the patients, when larger supplies of I^{131} were available, each single dose was 1000, 1500 or 2000 microcuries. To date, no single dose larger than 2000 microcuries has been given to hyperthyroid patients, although up to 50,000 microcuries have been administered at one time to a patient with metastatic carcinoma of the thyroid.

RESULTS OF THERAPY

Sufficient data are available on thirty-three patients to permit discussion of the effect of I^{131} in Graves' disease. Only a few had had recent treatment by other methods. None of the thirty-three patients had received x-ray therapy previously and only one patient (Case 8) had been operated upon previously; this patient had mild but definite

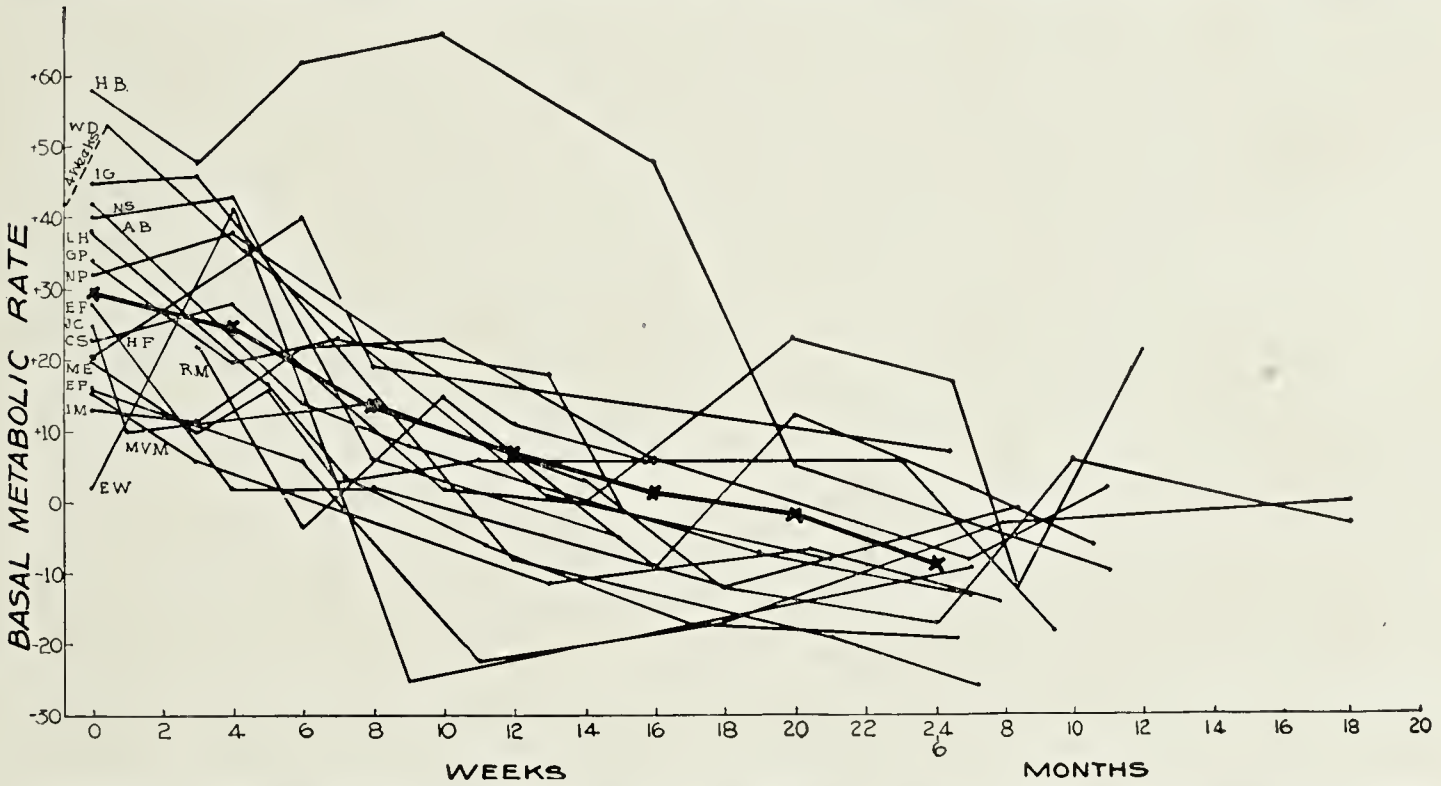

Fig. 1.—Composite graph of basal metabolic rates of 19 of 25 patients with satisfactory recovery following administration of radioiodine. (The remaining 6 patients were not included because time did not permit making a new chart.)

recurrence of hyperthyroidism following operation for which she was treated with I^{131}. Cases 7, 9, and 33 had received propylthiouracil until a few weeks prior to the administration of I^{131}; Case 18 had had thiouracil prior to radioiodine and Case 19 had been treated with ordinary iodine up to several months before radioiodine was given. Only Case 32 had any other specific therapy during the months subsequent to the administration of radioiodine—this patient had two episodes of rheumatic fever, one associated with rheumatic pancarditis and cardiac failure. She was given propylthiouracil in order to make doubly certain that her thyroid played no part in the cardiac complications even though her thyroid function seemed to have returned to normal within two and one-half months from the date of the first dose of I^{131}. The pertinent data concerning the thirty-three patients are summarized in Tables 1 and 2.

TABLE 1

Analysis of Twenty-five Cases in Which the Results Were Good

Name	Age	Sex	Estimated Thyroid Weight		Basal Metabolic Rates		Protein-bound Iodine, Mg. per 100 Cc.		Total Dose I^{131}, Microcuries	Uptake I^{131} in Thyroids	Time from Initial Dose of I^{131} to Return to Normal
			Before	After	Before	After	Before	After			
			Gm.	Gm.	Per cent	Per cent					Months
1. H. B.	47	F	40–45	Less than 15	+48	−10	14.75	4.8	4000	(60% first 1000)	4
2. I. B.	39	F	35–40	" " 30	+36	−22	12.0	5.1	3000	1600	2½
3. A. B.	58	F	30	8–10	+42	−13	9.4	5.3	1250		2½
4. J. C.	25	F	25	" " 10	+25	−16	9.9	4.1	1200		4¼
5. W. D.	65	F	25	" " 10	+53	−8	10.2	7.5	3000	980	3
6. M. E.	48	F	25	" " 5 (not palpable)	+20	−18	9.0	6.8	1400		2¾
7. H. F.	37	F	30	Less than 10	+20	+7	6.0 (?)	6.3	4000	2440	1½
8. E. F.	17	F	15 (post-operative recurrence	5 (barely palpable)	+16	−3	7.2	5.4	800		2½
9. E. F.	46	F	40	Less than 10	+28	−12		5.5	3500	1625	4
10. H. F.	52	M	30–35	10	+30	−4	14.3	6.2	2000		7½
11. I. G.	59	F	25–30	" " 10	+40	−26	10.0	5.5	2000	1000	3
12. F. H.	29	F	35	" " 10	+21	−11		6.9	4000	1540	2½
13. L. H.	57	F	35	" " 10	+38	−9	9.9	6.3	4000	1560	4
14. M. K.	44	M	25	" " 10	+22		11.0	5.2	2000	600	2
15. G. M.	9	F	20–25	10+	+22		17.4 (?)	5.2	2000	1462	3
16. C. M.	38	F	30	" " 10	+26	−1	12.0	5.4	2000	1360	2¾
17. M. V. M.	16	F	30–35	" " 15	+16	−14	12.8	7.6	2000	1300	3
18. R. M.	26	F	25	" " 10	+22	−6	10.1	5.2	2700		4
19. I. M.	46	F	30+	" " 10	+13	−8		5.4	2600	(30% last 1000)	6
20. E. M.	17	F	35	35	+26	−5	11.4	5.6	4500	2325	5
21. E. J. N.	9	F	25	12±	+2	−25	8.4	5.0	3000	600	5
22. N. P.	21	F	30	10+	+32	+6	8.0	4.6	4500	1350	4
23. G. P.	48	M	35	20	+34	−1	8.2	6.8	1450		4
24. M. S.	34	F	30–35	15+	+40	−5	11.7	4.9	3000	590	2
25. R. W.	16	F	35–40	25–30	+27	−13	11.9	5.2	4000	1840	4
Number of subjects			25	25	25	23	22	25	25		25
Average			31.2 gm.	13.3 gm.	+28%	−9.9%	10.7 mg.	5.7 mg.	2726 microcuries		3.6 months

TABLE 2

Analysis of Eight Cases in Which the Results Were Unsatisfactory

Name	Age	Sex	Estimated Thyroid Weight		Basal Metabolic Rates		Protein-bound Iodine, Mg. per 100 Cc.		Total Dose I^{131}, Microcuries	Uptake I^{131} in Thyroids	Time from Initial Dose of I^{131} to Return to Normal
			Before	After	Before	After	Before	After			
			Gm.	Gm.	Per cent	Per cent					
26. I. B.	47	F	35	10–12	+30	+3	14.0	5.0	4600	(1000 of last 2000)	16 months
27. V. C.	33	F	30	Less than 15	+50(?)		13.5	7.3	3850		14 months
28. E. C.	45	F	45	25	+53	+22	18.6		3600	(1200 of last 2000)	(Not well at 8 months—cannot be traced)
29. V. J.	41	F	60	Less than 35	+63	−7	16.0	8.4	5400	(1400 of last 2800)	12 months
30. H. L.	25	F	25–30	" " 8	+34	−12	8.0	4.6	4700	(1500 of 2450)	16 months
31. M. M.	19	F	50	30	+34	+33(?)	10.3	8.8	9150	(3600 of 6000)	(Not normal at 1 year)
32. H. R.	35	F	50	25–30	+56	+40(?)	14.6	7.2	4000	(2500)	2½ months (Acute rheumatic pancarditis. Confused picture)
33. C. S.	33	F	40	20+	+23	−12	8.3	6.9	9000	(3925 of 7000)	(Not normal at 1 year)
Number of subjects...			8	8	8	7	8	7	8		
Average.....			42.5 gm.	22 gm.	+43%	+9.5%	12.9 mg.	6.9 mg.	5537 microcuries		

Thyroid weights were estimated by one individual (M.H.S.) who for about twelve years, has estimated the size of thyroids of many patients who were to be thyroidectomized. The thyroid tissue removed at operation has been weighed and compared with the preoperatively estimated weight. To determine the weight of thyroid left in the neck, a piece of the removed thyroid, the size and shape of the residual in the neck, is weighed. The accuracy of thyroid weights as estimated by these procedures has been such as to lend credence to the recorded size of the thyroids of these thirty-three patients before and after treatment (Tables 1 and 2).

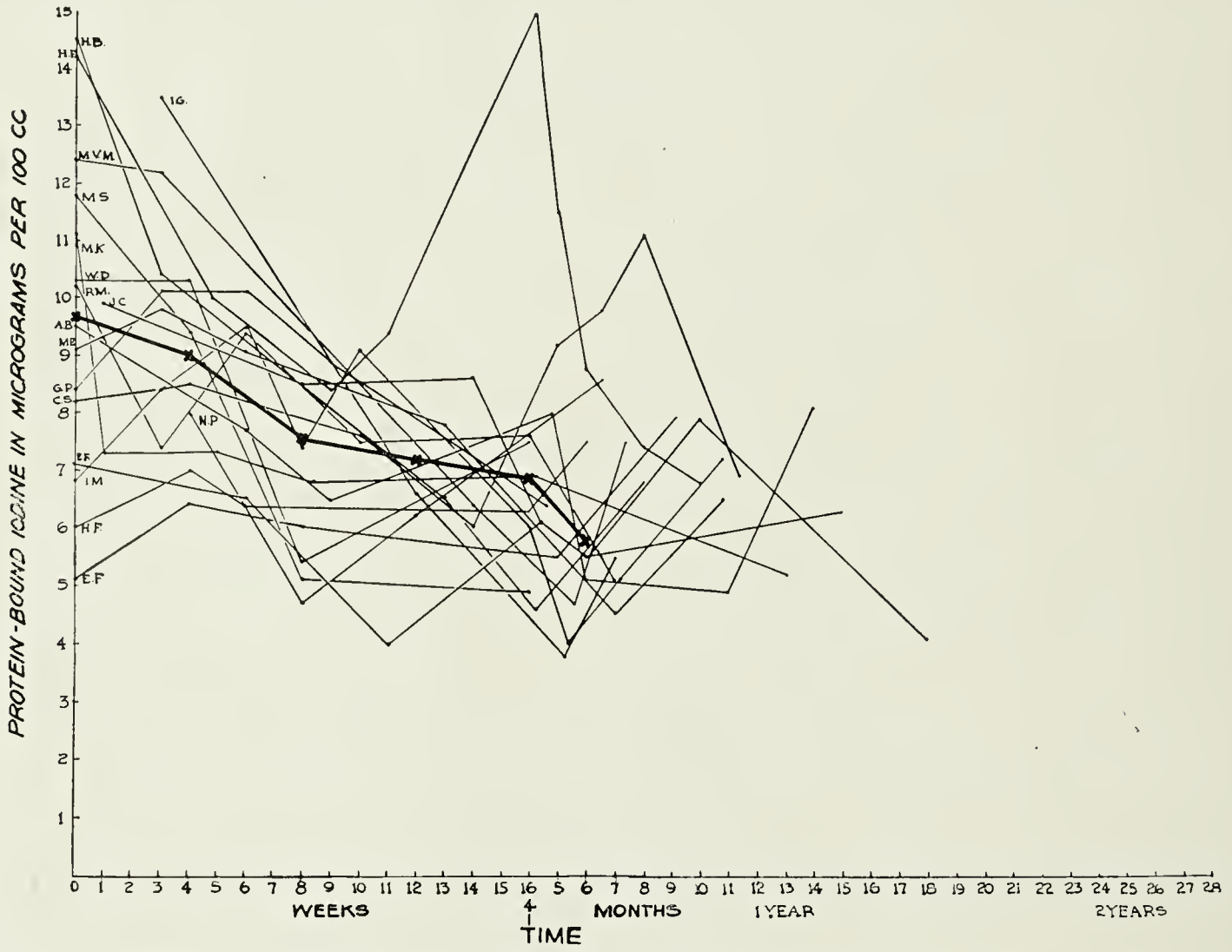

Fig. 2.—Composite graph of protein-bound iodines in 19 of 25 patients with satisfactory recovery following radioiodine therapy.

The blank spaces noted in Tables 1 and 2 under the tabulation of basal metabolic rates and protein-bound serum iodines represent either a failure to obtain a test at the time the patient was studied or the elimination of an unsatisfactory test. As always happens in a study such as this one, few tests could not be done and a few tests were known to be unsatisfactory by both the technicians doing the tests and (as in the case of a basal metabolic rate determination) by the patient himself.

The last column of Table 1 shows, for the first twenty-five patients, the time interval between the date of the first dose of I^{131} and the date when the patient was clearly normal by history, physical exam-

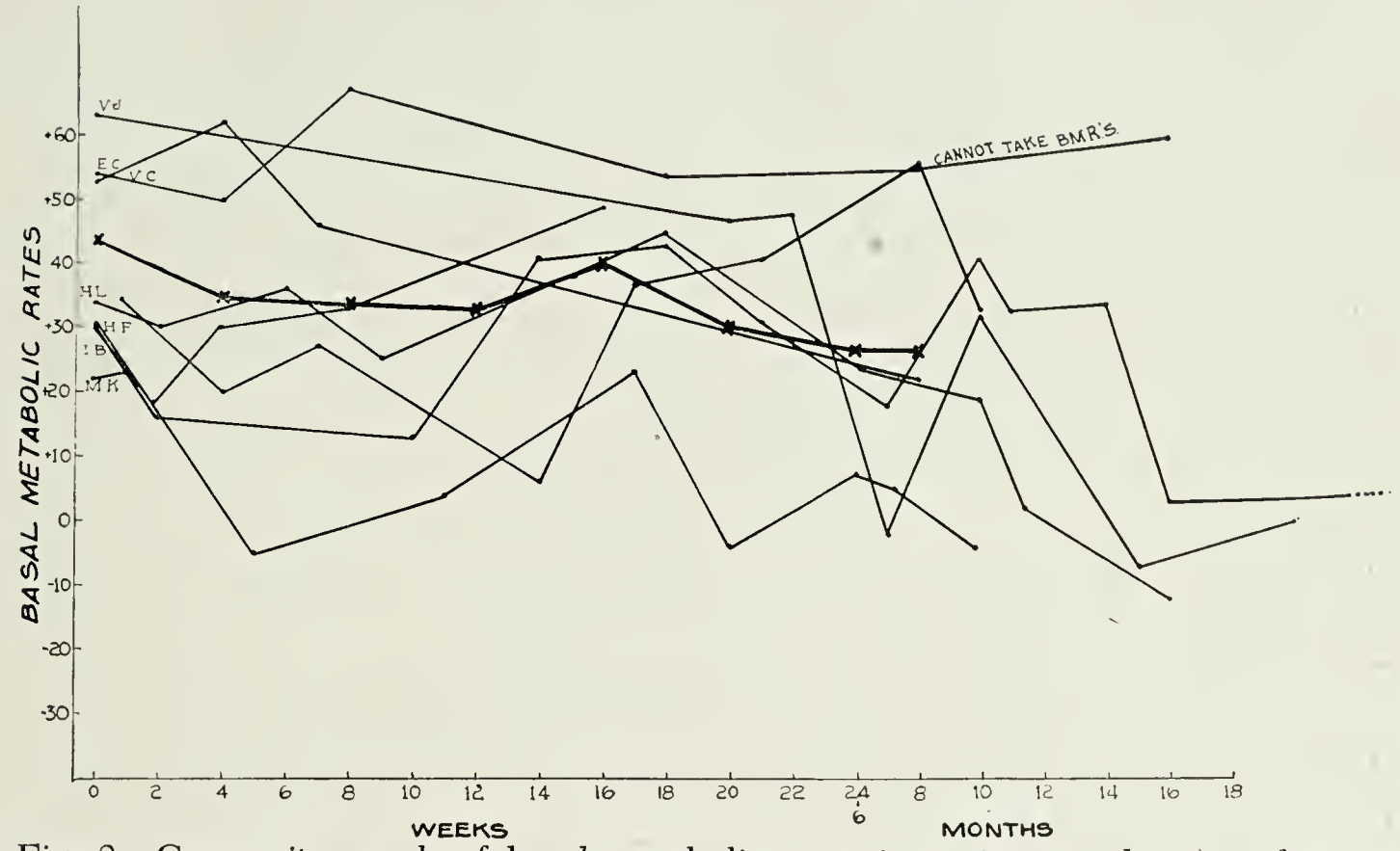

Fig. 3.—Composite graph of basal metabolic rates in patients with unsatisfactory recovery.

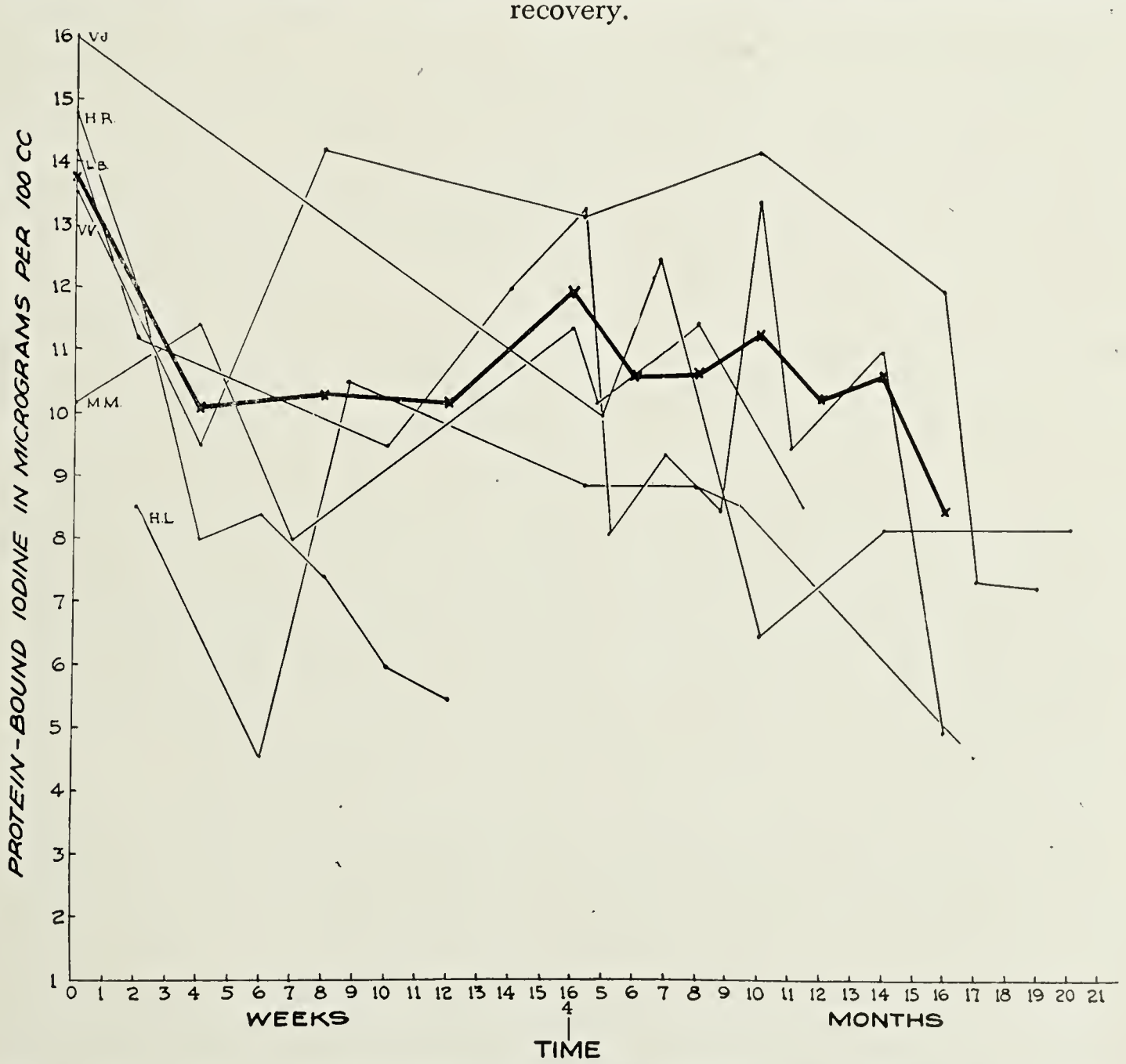

Fig. 4.—Composite graph of serum protein-bound iodines in patients with unsatis factory recovery.

ination and laboratory tests. Patients 26 through 33 have in some instances not yet returned to normal status, so only the statement that they are not normal after a given period of follow-up is made.

Of the thirty-three patients, what may be classified as good results in the sense that the patients returned to normal in about four months (average 3.7 months) were obtained in twenty-five; the thyroids in this same interval decreased from an average of just over 30 gm. to less

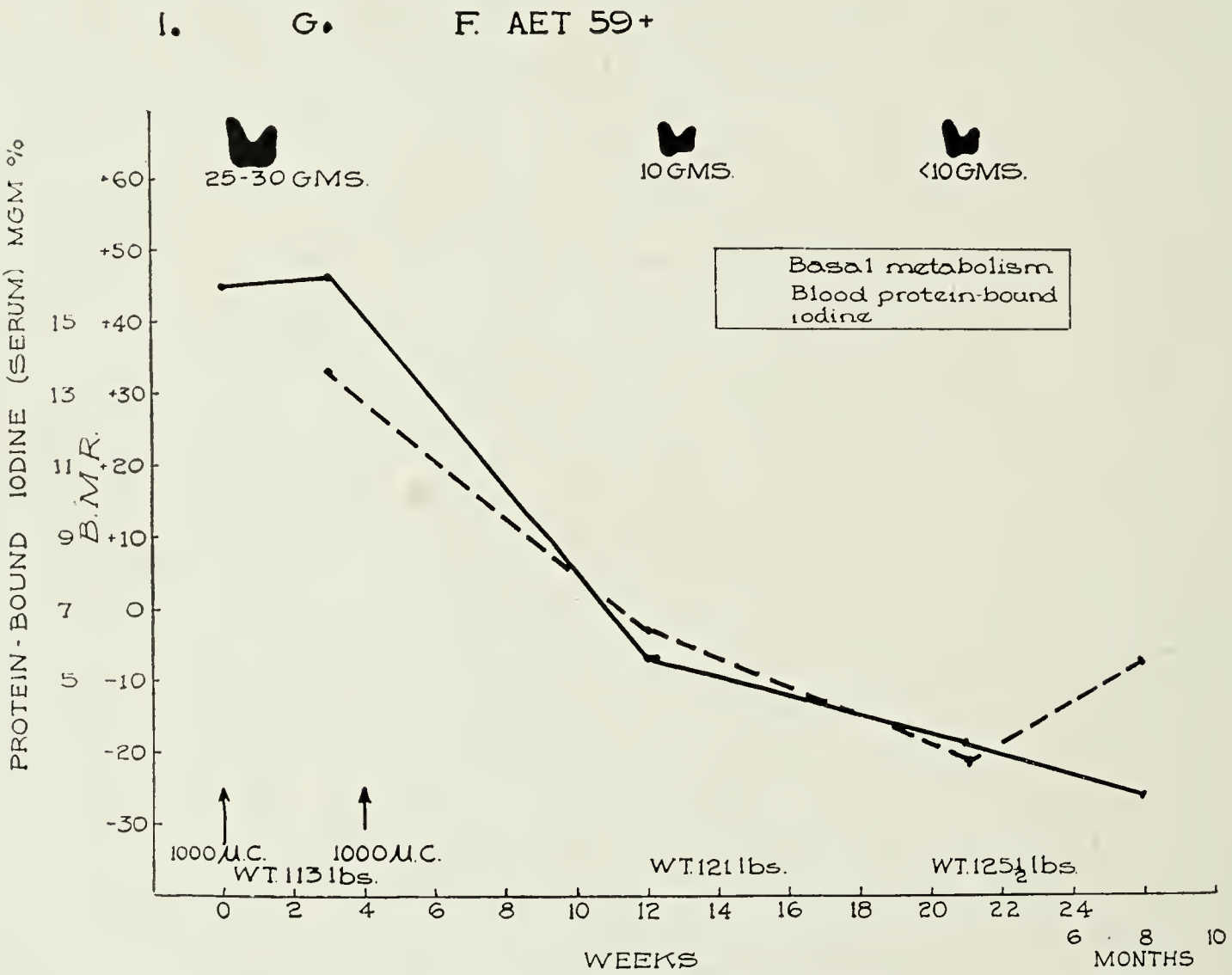

Fig. 5.—Course of Case 11. Patient I. G., a 59 year old housewife, who had had periods of nervousness, irritability, rapid and regular heart rate with sudden onset and offset since the death of her husband in 1942. Pneumonia had followed repair of a detached retina in October, 1945 and was associated with a thyroid crisis. Mrs. G. was a flushed, warm, hyperactive woman with a stare, no exophthalmos, a pulse that was 90 and regular, a blood pressure of 180/100, a thyroid estimated to weigh between 25 and 30 gm. with no nodules or bruit, an enlarged heart with a mitral systolic murmur, and a fine tremor of her extended fingers.

than 15 gm., the basal metabolic rates dropped from an average of plus 30 per cent to an average of minus 10 per cent, and the protein-bound iodines (determined on blood serum) dropped from an average of 10.6 micrograms per 100 cc. to 5.7 micrograms per 100 cc. The average total dose of I^{131} was 2726 microcuries.

Of the eight patients (Table 2, Cases 26 to 33) in which the results were classified as unsatisfactory, three have not yet returned to normal; one is so handicapped by rheumatic pancarditis that her clinical

situation cannot be appraised satisfactorily; and four patients took too long a period to return to normal. On the whole, these patients had larger goiters (average 43 gm.), higher basal metabolic rates (average

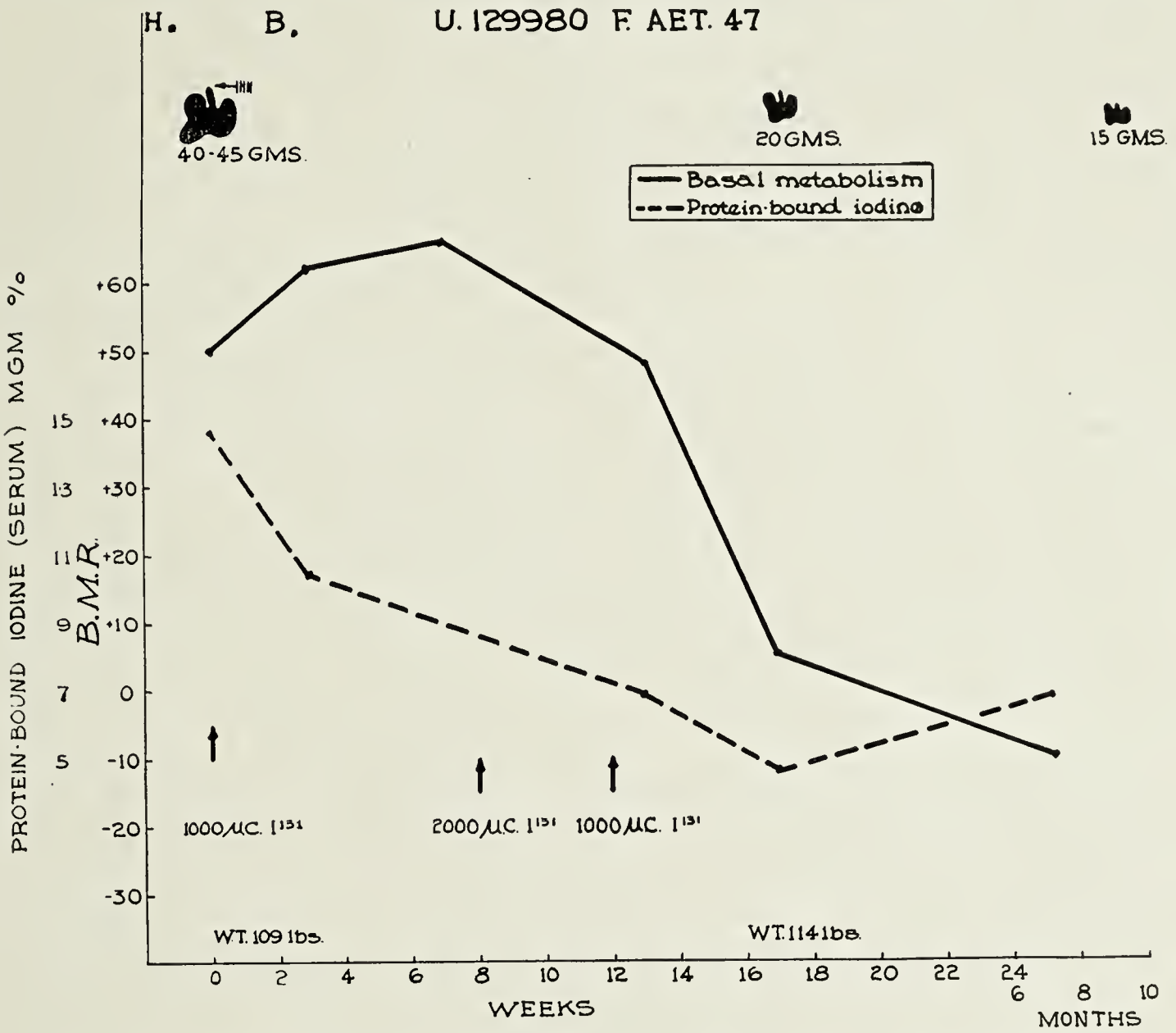

Fig. 6.—Course of Case 1, illustrative of a good result in moderately severe Graves' disease. Patient H. B., a 47 year old office worker and housewife, whose symptoms began one year before entry to the University of California Hospital with the gradual onset of nervousness, irritability, tremor and an enlarged thyroid. These symptoms progressed and six months before entry she noticed increasing heart consciousness and dyspnea on exertion, poor appetite, increased sweating and an increase to 2 to 3 stools daily. On physical examination, Mrs. B. was apprehensive but cooperative, moving and talking rapidly. The skin was warm, flushed and moist. Exophthalmos was apparent and measured 19.5 mm. on the right and 20.5 mm. on the left; the orbital resistance was increased, lid lag was definite. All her teeth had been removed. The thyroid was enlarged to about 45 gm.; a systolic bruit was heard bilaterally and a pyramidal lobe was palpable. The heart was normal except for overactivity, the pulse was 100 and regular, and the blood pressure was 130/70. The tip of the spleen was palpable. A fine tremor of the extended fingers was present.

plus 43 per cent), higher protein-bound iodines (average 12.9 microcuries) than Cases 1 to 25. In the beginning of this study, we did not know the dose needed in these sicker patients and, both then and later, often did not have adequate amounts to give them. Under our present

system, such patients would be given doses of at least 2000 microcuries of I^{131} at least once a month until the clinical status was nearing normal and the thyroids had shown a decrease in size toward the normal. We would estimate the largest total dose necessary for any of this group of eight patients to be between 10 and 12 millicuries.

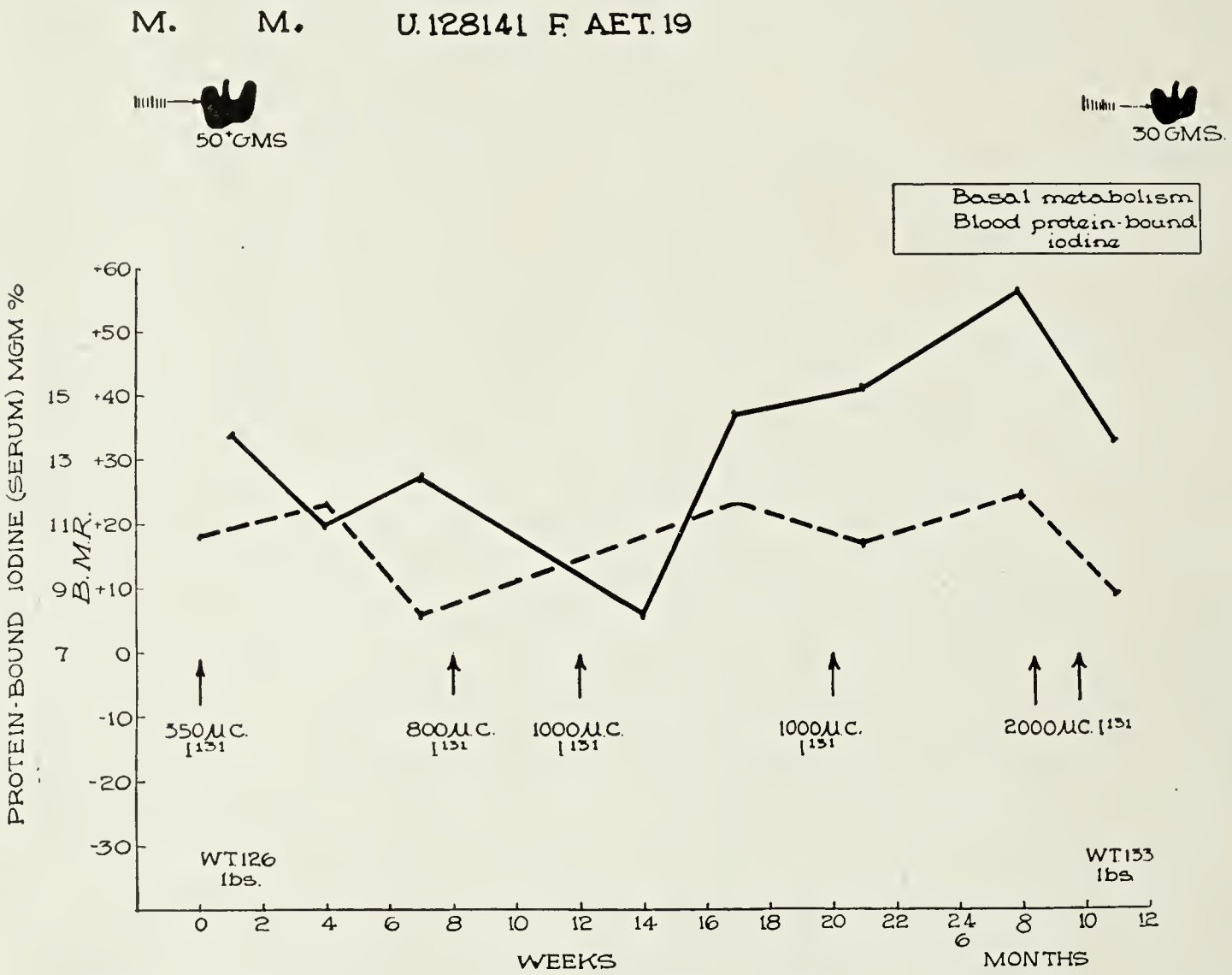

Fig. 7.—Case 31. Mrs. M. M., a 19 year old housewife, whose symptoms began ten months before entry following a fire in her living quarters. She had noted nervousness and decrease in menstrual flow progressing in the next five months to greater irritability, and by two months before entry she noticed a goiter, pounding heart and increased fatigability. A basal metabolic rate six months before entry was normal. Her paternal grandmother had had a goiter treated with iodine. On physical examination, Mrs. M. was flushed with warm moist skin. There was a stare, exophthalmos (both eyes measured 20.5 mm.), widened palpebral fissures and lid lag. The tonsils were absent. The thyroid was enlarged to about 50 gm., the right lobe felt larger than the left and there was a bruit, both systolic and diastolic, on the right and systolic on the left. A pyramidal lobe was palpable. The heart was normal in size with soft mitral and pulmonic systolic murmurs. The pulse was 120 and regular; the blood pressure 135/65. There was a right rectus scar. Her extended fingers showed a fine tremor. She is classified as an unsatisfactory result.

Certain changes were noted in enough patients following treatment with I^{131} to warrant comment. Often within twenty-four to seventy-two hours after the radioiodine had been given, there was definite tenderness in the thyroid, sometimes noted spontaneously by the patient but nearly always apparent (after a dose of 2000 microcuries)

when the thyroid was palpated. With this, the sedimentation rate increased to as high as 35 mm. (Wintrobe). Also there was an increase in the level of the protein-bound iodine and from the fourth to the tenth day or longer an increase in the symptoms of hyperthyroidism. More complete studies will be published concerning these phenomena—at the present time we believe they indicate destruction of the thyroid from radiation and release of its previously stored hormone. Failure to find these changes may mean that relatively small amounts of radioiodine were taken up by the thyroid or that little hormone was stored within the thyroid at the time the radioiodine was given. In severe hyperthyroidism, large doses of radioiodine may even precipitate a serious exacerbation.

Twenty-six patients of the thirty-three had serial measurements of the prominence of their eyes. One patient had a decrease in exophthalmos of 1.5 mm. in one eye and no change in the other. Seventeen patients showed no change in the prominence of their eyes. Six others had increases of 1.5 to 2.5 mm. Two patients developed severe exophthalmos, Case 1 having an increase of 3.5 mm. in the prominence of both eyes and Case 3 an increase of 4.5 in the right eye and 4 in the left eye as measured by a Zeiss Hertel Ophthalmometer. Both of the patients with severe exophthalmos were placed on thyroid therapy to tolerance; in Table 1, tests recorded for both extend only to the time of thyroid therapy. In our experience at the University of California Hospital to date, an increase in exophthalmos in patients treated with radioiodine occurs less frequently than in surgically treated patients and more frequently than in patients treated with x-ray.[8]

While the investigators at the University of California Hospital have had little experience with patients followed for many years after radioiodine therapy, three of Hamilton and Soley's patients[2] have been examined repeatedly since 1941. Six patients were treated in that original series; one died soon after her first dose of radioiodine from a cerebral embolus caused by an attack of paroxysmal auricular fibrillation; two others moved away before therapy was completed and one of these is known to have had a subtotal thyroidectomy later in New York. The remaining three patients have done well. Two received 1000 microcuries and the third 1500 microcuries. The third patient had received 1000 microcuries in divided dosage of 500 microcuries each about one month apart but required a third dose of 500 microcuries to bring about a complete remission. One of these three has what might be classified as doubtful hypothyroidism. Of the other two who have remained normal, one is being followed by another physician in Kansas.

COMMENT

The only radioactive isotope of iodine used in the therapy of Graves' disease at the University of California Hospital is Iodine^{131}. This should be stressed since Hertz and Roberts,[3] and Chapman and Evans[4]

have used mixtures of I^{130} and I^{131}. I^{130} has a half life of twelve and one-half hours; one microcurie uniformly distributed in one gram of tissue will, during the course of its complete decay, deliver 12.45 equivalent roentgens of beta ray energy. On the other hand, I^{131} has a half life of eight days; one microcurie uniformly distributed in one gram of tissue delivers 142 equivalent roentgens of beta ray energy during the course of its complete decay.[9] It is apparent that much larger doses of I^{130} than of I^{131} are needed to irradiate the thyroid sufficiently to cause a satisfactory remission in hyperthyroidism. This should be kept in mind when the various published reports on radioiodine are read.

Proper total dosages of I^{131} and ideal treatment schedules for its administration are not yet known. The Massachusetts General Hospital group and the group at the Mayo Clinic are using much larger single and total doses than the group at the University of California Hospital. The exchange of data among these and other groups and the fact that at present only I^{131} is being used by all groups will facilitate the clarification of the problem of dosage. No one yet knows whether a single dose of 12 millicuries is more effective than, for example, three doses of 4 millicuries or six doses of 2 millicuries. There will remain the problem of exact measurement of a millicurie of I^{131} which in part is being solved by exchange and measurement of samples of this isotope.

Up to the present time in this study we have not been able to determine by any of the data at hand, such as thyroid size, basal metabolic rate, protein-bound iodine, or any combination of these or other objective data, what the dose of radioiodine should be to control a particular patient's disease. Clinical judgment has been the most important factor in deciding what dose is to be used. Doses of 1 to 4 millicuries are apparently adequate for the treatment of mild to moderate Graves' disease whereas 10 to 12 or more millicuries are needed for severe Graves' disease.

SUMMARY

Thirty-three patients with Graves' disease have been treated with orally administered radioiodine (I^{131}) and have been re-examined for periods of three months to two years. The smallest dose of I^{131} which produced a satisfactory remission was 800 microcuries; the largest 9150 microcuries. Our present treatment schedule comprises the administration of 2000 microcuries initially and repetition of similar doses at monthly intervals until the total required dose has been given. Seventy-five per cent (twenty-five) of the thirty-three patients have had a satisfactory remission of symptoms and signs of hyperthyroidism in from one and one-half months to seven and one-half months from the start of therapy. Eight patients (25 per cent) have either taken too long to return to normal (up to sixteen months) or have not returned to normal within the period of observation (up to one year) so that their treatment has been classified as unsatisfactory. Studies of specific

problems of dosage, measurement of radioiodine and distribution of radioiodine in the thyroid indicate that further experience is necessary before conclusions can be drawn as to the place of this type of therapy in the treatment of Graves' disease.

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TESTOSTERONE IN THE TREATMENT OF BREAST CARCINOMA*

Frank E. Adair, M.D., F.A.C.S.†

REVIEW OF THE LITERATURE

Because of the great interest today in the treatment of human breast cancer with the androgens, it may be profitable to bring together the entire literature on the subject for consideration.

Testosterone has been used in cases of mammary carcinoma in the form of testosterone propionate by intramuscular injection,[1, 2, 3, 4, 5, 6, 7, 8] by subcutaneous implantation of crystalline testosterone pellets,[1, 2, 8] as testosterone acetate by intramuscular injection,[9] and as methyl testosterone orally.[10]

The first reported cases are evidently those of Loeser,[7] who treated two women with proven recurrences of carcinoma following mastectomy, using testosterone propionate intramuscularly. One was a 37 year old nullipara with an infraclavicular recurrence seven months after operation, to whom he gave rather modest amounts of testosterone propionate for more than a year; she developed no further recurrence during the twenty-two months, after the first recurrence, which were covered by the report. The other patient was a woman of 42, gravida I, para 0, whose cancer reappeared in the scar and in the supraclavicular nodes five and fourteen months, respectively, after mastectomy, and who showed no further recurrence for twenty-one months after the latter one while receiving moderate amounts of testosterone propionate. Loeser mentions that male hormone was used originally to relieve the menorrhagia in these women, and that the effect on recurrences of carcinoma was observed incidentally. He acknowledges that the period of observation was too short to admit of any conclusion but does state that the results were striking and quite possibly significant.

Ulrich's[9] report, appearing in the same pages, includes two cases with problematical features such as uncertainty of diagnosis, brief observation, low dosage of male hormone, and concomitant oophorectomy; but this author nevertheless expresses some enthusiasm. One

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From the Breast Department of the Memorial Hospital.

* Read at the International Cancer Congress, St. Louis, Missouri, September 5, 1947.

We are indebted to the Schering Corporation for supplying us with testosterone (Oreton) propionate; and to Dr. Edward Henderson of Schering, for generous aid in certain technical phases of our work.

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patient was a woman of 45 who had had radical mastectomy, and whose other breast was cystic. Ulrich contended that the original carcinoma had developed on the basis of chronic cystic mastitis and that a new malignancy was therefore liable to develop in the other breast. He administered an uncertain quantity of testosterone acetate and found improvement both in the lymphedema of the operated side and in the pain and nodular consistency of the cystic breast, sufficient to dissuade him from a second mastectomy. In the other patient, aged 42, carcinoma was obvious clinically in one breast while the other contained two tumors without associated lymph nodes. Castration was done, and a "course" of testosterone acetate was given then and a month later. Ulrich asserts that within five weeks there was visible diminution in the size of the malignant tumor, and that it had "passed back within the limit of operability" (d'inopérable qu'il fut, il est passé à la limite de l'opérabilité), although he was so much impressed that he was deferring operation even then. Unfortunately, it is not possible to deduce the length of time this patient was followed.

Loeser[11, 12] reported several additional cases, summarizing them[8] in 1941 when six patients are described. Two were treated with progestins, and of these one received progestins alone. Of the five receiving male hormone (in a combination of intramuscular injections and subcutaneous implantations in most cases), three survived at least to the time of the report, one improved for a brief period, and one deteriorated rapidly. They represented women who exhibited soft-tissue recurrences one-half to two years after mastectomy, at ages of 37 to 45 years, and one woman of 60 who had been treated with radium for eight years. In the favorable cases, as Loeser points out, the recurrence was first removed surgically or destroyed by x-ray, so that cancer was not obviously present at the time testosterone was begun. This investigator adopted the policy of renewing the treatment whenever the masculinizing effect was evidently wearing off, so that three younger cases received subcutaneous implants of 500 to 600 mg. of testosterone about every six months. The older, unoperated patient was given a fairly large intramuscular course and exhibited clear local and general improvement for several months before declining again; further treatment was not possible at that time due to the wartime shortage of the hormone. Even the fifth case "showed striking symptoms of improvement," which may signify a gain in weight and improvement in general condition, but new neoplasms appeared, involving the other breast, and the use of progestin exerted no influence that was evident in the patient's downhill course. The surviving patients were almost five years postoperative at the time of the report, and the administration of male hormone had been attended by an absence of further recurrences for two and one-half to four years. Loeser believes that the mode of action of male hormone may be explained as a "neutralization" of estrogen.

Farrow and Woodard[3] in 1942 reported three cases in detail of their series of thirty-three patients who had received testosterone therapy. Using 5 to 25 mg. of testosterone propionate one to three times weekly for ten to twelve doses, they were able to secure relief of pain in half their cases, but the neoplasms were not influenced at this dosage. The three cases were chosen as exemplifying an adverse effect of male hormone therapy, viz.: an increase in the serum calcium, from high levels of 10 to 11 mg. per 100 cc. to 15 mg. or more per 100 cc., with the production of headache, anorexia, nausea, vomiting, stupor, hot flushes and increased pain at the site of osseous lesions. Decalcification as seen by x-ray was said to have been aggravated. No clinical benefit was apparent. In these patients, not only testosterone, but also estrone, and even x-ray therapy, produced an increase in serum calcium. This is the one untoward action which has been reported to occur in any of the cases treated with testosterone propionate. There was related, but moderate, rise in phosphatase. Farrow and Woodard suggest that the effect of testosterone in such cases is increased osteolytic activity of the neoplasm under an "activating" influence of the hormone. These authors concluded that testosterone propionate is contraindicated in mammary cancer, in the dosage used in their study.

A word of explanation needs to be injected here concerning the reported action of testosterone propionate in causing an increase in the serum calcium in patients with carcinoma of the breast metastatic to bone. It is well known that these patients almost invariably show a high serum calcium before treatment of any kind. If testosterone propionate were capable of causing directly an increase in serum calcium in cases of breast cancer with bone metastases, as reported by Farrow and Woodard, then one would have to conclude that it would do it in all cases. This is certainly not true in our later series of cases which have been very carefully followed. In cases with moderate bone involvement, not only is there no increase in serum calcium, but there is, in fact, a slight decrease under testosterone therapy. In cases with widespread bone involvement where the initial serum calcium is high, we have occasionally noted a rise in the serum calcium following the institution of testosterone therapy, but it is quite possible that rise may be transitory and due to the effect of testosterone on the healing process. Bone lesions, like any other lesion, heal from the bottom upward. As new bone cells are being laid down in the deeper recesses of the lesion, it is reasonable to assume that the necrotic cells occupying the surface of the wound would be literally displaced by this healing process and therefore liberated into the blood stream. A very careful study of the metabolism of testosterone in noncancerous patients fails to show any action leading to an increase in serum calcium. We have arranged to study this problem very carefully on a large series of cases and will be prepared to report definite findings at a later date.

Fels,[4] in 1944, described three women showing favorable responses

during a short period of observation. Two were women with osseous metastases after mastectomy, at ages of 34 and 48, of whom the former showed x-ray evidences of recalcification within four months of beginning testosterone propionate, and the latter may or may not have had less pain but at all events ceased vomiting after a few weeks of treatment. The third patient was an older woman with radiologically treated cancer en cuirasse then undergoing local extensions; it is not clear that any prominent effect was obtained.

Prudente,[13] in 1945, reported the use of testosterone propionate for inoperable mammary cancer, mainly as an anodyne and in fairly low dosage. In addition, he formed a comparison between patients who did and did not receive male hormone prophylactically after mastectomy, when mastopathy was present in the remaining breast. After four years twelve treated cases were compared with sixty-four untreated, with the finding that patients without axillary metastases are likely to survive four years with or without treatment, but that patients *with* metastases are twice as likely to survive if they are treated with even small doses of testosterone propionate. Prudente used up to 175 mg. weekly by intramuscular injection.

Of less significance, although interesting, is Prudente's comparison, after three years, of treated and untreated patients according to the grade of malignancy present. He reports the three year survival of one of three patients with grade IV neoplasm, which is merely suggestive; but some real significance attaches to the grade III cases, in which the patients are three times as likely to survive if they receive testosterone. There is also a real, although less prominent, advantage in testosterone treated carcinoma of grade II, although such cases have a noticeable chance of surviving in any event. Grade I cases, in which patients are usually able to survive for three years, regardless of treatment, afford no real comparison.

Prudente furnishes the details of six cases exemplifying forty-nine women followed one year, out of a total of sixty-three women given postoperative testosterone for clinical grade I and II malignancy, although five of the six are defined as pathological grade IV. Most of the cases received only small doses and pursued rapidly fatal courses; it appeared to be Prudente's rather curious policy to reduce or discontinue the androgen when amenorrhea ensued, or when arrhenomimetic signs appeared. Notwithstanding, one patient with grade II malignancy survived extraordinarily long, after refusing operation until the fourth year of the disease, even with such modest amounts as 30 mg. of testosterone propionate per week. It might be questioned whether any influence could have been thus exerted, except that a pathological study of the excised primary tumor showed an unusual fibrotic encapsulation of whatever nests of neoplastic duct tissue occurred, while the remainder of the breast was atrophic. The last of these cases continues under study, about two years after mastectomy and several

months after bony and lymphatic recurrences, which were not prevented by 75 mg. of male hormone weekly for more than a year. This brief series, chosen somehow from a much larger material, does not correspond well with the more favorable findings given in statistical form, but does provide an interesting study in low-dosage androgen therapy.

In 1946, Boger[10] reported his treatment of a single case of mammary cancer using methyl testosterone by mouth, starting at 30 mg. daily. The case exhibited several discouraging features, such as neglect, a simple mastectomy and permitting the patient to become pregnant. Oophorectomy was done in the presence of multiple bony metastases twenty months after mastectomy. Methyl testosterone was begun after castration and continued for six months. The result of the surgical and "endocrinological" castration was a disappearance of pain, gain in weight, renewed ability to work, recalcification of some metastatic lesions, and general improvement; but two months after terminating the androgen the patient incurred new metastases and soon expired. The published literature relating to methyl testosterone is apparently limited to this single case. It may be a permissible inference that this case suggests an action of this compound quite comparable with that of testosterone esters.

Experience of the Memorial Hospital.—Although we had been working on the problem for a number of years, the first detailed report of our Memorial Hospital group did not appear until 1946[2] and even then did not provide the late follow-up that might be desired in the eleven cases mentioned in detail. Later reports provide further information concerning some of our original cases and further confirm the beneficial effects of testosterone in a small series of new ones.[1, 6] In our first paper we presented four cases in detail as exemplifying favorable results after testosterone propionate by injection alone or by injection and subcutaneous implant, the dosage in this series being significantly high for the first time in the literature.

However, from my experience in treating forty-eight private patients in 1944 using 25 mg. of testosterone propionate daily, I had come to three conclusions, namely:

1. That in the occasional case with painful bone metastasis this agent was nothing less than miraculous for the relief of pain and for giving the patient needed rest without narcosis.

2. There is marked selectivity of action. In one case the improvement was striking, while in another the improvement, especially in local recurrence and soft tissue metastasis, was not impressive except in the occasional case.

3. Larger dosages should have been employed, experimentally, in spite of the high cost of the product at that time.

In our 1946 series one patient was of the postmenopausal type with only soft tissue metastases; the tumor had not been removed, and both

the involved breast and the associated lymph nodes changed visibly under treatment. Masses disappeared and the nodes were no longer palpable. Unfortunately the patient became inaccessible, which precluded adequate treatment and follow-up. The other three cases exemplified younger (age forty-two to forty-seven) patients with bony metastases, which began to recalcify in all three under treatment, while pain and other complaints disappeared. Additional treatment included previous roentgen castration and local use of x-ray for metastases apart from postoperative routine. The youngest patients became amenorrheic and had virilizing signs. As long as these patients were followed, about a year after admission, they were surviving in an improved condition.

Our group later reported[5] more definitive results in patients with soft-part metastases, only two of six cases indicating a clear improvement. They include an unusual series of patients, for example, a woman of 52 with inoperable carcinoma treated by x-ray, a young patient seen in quite advanced disease, a patient of 54 who apparently watched a mass in the breast enlarge and ulcerate over a period of seven years, and so on. The latter case illustrates an indifferent effect of testosterone given for five months, followed by complete regression induced by x-ray. Another patient illustrates what may be an optimal effect of male hormone, given because of lymphatic and pulmonary metastases appearing two years after mastectomy. After 6400 mg. of testosterone propionate in six weeks, the cough had disappeared, the nodes were no longer felt, and films of the chest showed diminution in the size of the pulmonary lesions. This patient was symptom-free for at least two months of observation. The other four patients deteriorated at different rates, although some action of the male hormone was apparent from amenorrhea or anestrous smears. Changes in the neoplasm were sought histologically in four of the cases but not found; when amenorrhea was induced in these women, even with large doses of testosterone, it was comparatively brief; but the usual grade of andromimetic response was found—indicating that in some respects, though not all, the male hormone was able, with difficulty, to effect the characteristic responses; it is rather as if its action were "resisted" in some tissues.

Impressions from the Literature.—It is evident from the detailed case reports of the literature mentioned that certain desirable information is lacking in many reports, and that no great uniformity is present as to details. Even the important general impressions about mammary cancer can only be suggested from the data, since the numbers are small, but they are fairly well borne out in a nonstatistical way; for example, a fairly large proportion of the women are noted to have had menometrorrhagia; several familial histories of cancer are present; older patients did not usually have bony metastases (except in such cases as a woman who was menstruating at 58) while younger patients did; nulliparae are prominent in the series; and there is the perplexing

tendency of patients to survive for long periods with untreated or improperly treated cancer, even before they come under consideration in the problem of testosterone therapy, which they thus confuse.

The tendency of some observers to draw either optimistic or pessimistic conclusions following the administration of small dosage which covered a very short period, is obvious.

Of outstanding significance is the observation of Loeser[8] that there is a possibility of forestalling the reappearance of cancer in patients in whom all known neoplasms have been eliminated, surgically or by x-ray, as in his cases, if male hormone is then given. But, within the limitations of follow-up, there are several patients in whom neoplasm existed but was kept under control sufficiently well to hint at survival; and in one especially interesting case there was no appreciable response to androgen but remarkable benefit from x-ray employed following it. It is suggested that a potential response occurred in this case, that pretreatment of the tumor with testosterone may have influenced the eventual favorable response to x-ray; however, this theory remains to be proved.

In general, every possible result has been seen in these cases. Adverse effects are evidently limited to the hypercalcemia noted by Farrow and Woodard[3] and Adair and Herrmann[2] which, in the light of later knowledge, may or may not be directly caused by testosterone. Arrhenomimetic actions, amenorrhea, and occasionally edema are peculiar to androgenic therapy in women and are of no great consequence, considering the seriousness of the disease being treated.

BASIS OF THE PRESENT REPORT

Many new problems are constantly being presented as our experience increases. At the present time our impressions are based on our experience with approximately 450 human cases treated with testosterone propionate by intramuscular injection, pellet implantation or methyl testosterone by mouth. The cases are divided as follows:

48 private patients treated in 1944 and 1945.
85 research clinic patients.
217 patients operated by radical mastectomy; and at the time of operation 300 mg. placed in the operative wound in pellet form.
53 private patients treated 1946 and 1947.
45 patients treated by doctor friends under my guidance.

PHYSIOLOGICAL ACTION

The 217 patients who had four testosterone pellets of 75 mg. each placed in the latissimus dorsi muscle at the time of operation gave us an opportunity to study the effect of the agent in the human when given in one massive dose.

Menstruation.—Approximately half of the patients were postmenopausal. The medication seemed to have no effect on bringing on uterine bleeding, or lower abdominal discomfort.

The patients who still menstruated varied enormously in their reactions to the same dosage. However, the age of the patient obviously had a determining effect in the time lapse of menstrual cessation. It depended on the phase of the menstrual cycle, in which the hormone was administered, as to whether or not there would be another menstruation. The patient may or may not have one more period before she started to skip. The younger the patient, the shorter the duration of skipping; this in the young meant that two to four periods would be skipped before returning to normal. There were a very few of the younger women who never missed a period; but this is against the rule. The nearer the age of the patient to the menopause, the longer seemed the duration of skipping. Some skipped as long as six months; a few, longer; some never regained their menstrual periods. In other words, about the time of the menopause testosterone can be a means of effecting a true menopause.

Hirsutism.—The production of an excess of hair on the face and body is a fairly constant reaction to androgen administration. Those women with fair soft skin and light complexion produce less of a hair growth. In dark haired and complexioned women, however, the growth of hair over the face, lips, chest and legs is sometimes very heavy and most embarrassing for the patient. Some women shave daily; and some use a depilatory. On cessation of androgen administration hirsutism is improved, but in certain instances it persists for many months after cessation of administration.

Voice Changes.—Deepening of the voice associated with huskiness characterizes the changes secondary to androgen administration. This change can be produced either by the one massive dose, or is more consistently produced by prolonging the administration of the agent. The changes are due to two causes, namely, the thickening of the lining membrane of the larynx, and a thickening of the thyroid cartilages which characterizes the change which takes place at puberty. The voice changes persist for many months, although there is improvement which takes place when androgen therapy ceases. Occasionally the voice closely approximates that of the male voice. Voice changes take place in women at all ages who are under androgen therapy.

Libido.—An increase in sexual desire takes place at all ages except in those of about 60 years and older. We have seen increased libido in women who are ten years past their menopause. The degree of increase varies enormously with the individual. In cases of continued administration of the androgen it at times became quite a difficult problem to handle. In those who are unable to sleep it becomes necessary to give fairly heavy sedation, and also to apply a local sedative ointment to the clitoric area.

Acne.—The acne of the face, chest, back and legs is a less constant reaction than the other secondary reactions. It is an accompaniment of the hair growth with irritation and secondary infection; such as is seen at puberty. In some extreme instances it becomes quite a problem. The condition subsides with the withdrawal of the hormone.

ACTION OF TESTOSTERONE

Aside from the above virilizing influences, and improvement in general health, testosterone has obviously two influences on cancerous breast tissue either primary or metastatic. These actions are quite unpredictable.

The Direct Effect on Cancerous Tissue.—We know by experience that we do obtain regression of the primary tumor and its metastatic nodules, but unfortunately only rarely. In our original presentation of case I, *Annals of Surgery*,[2] there was a massive diminution of the original breast cancer together with the axillary mass, disease within supraclavical spaces and nodules over the right scapula and upper abdominal wall following testosterone therapy. This was a direct effect on cancer tissue.

Another example of this direct effect is the case of a woman on whom I did a radical mastectomy, and who later got metastatic disease in the lining of the uterus proven by curettage and microscopic study. The uterine bleeding was so profound that her hemoglobin was at approximately 40 per cent and she was very weak and sick from loss of blood. Her bleeding was rather promptly terminated by placing her on testotserone therapy; and she has had no more bleeding since—a period of about seven months. Her hemoglobin is back to normal, and there has been no obvious progress of her metastatic disease.

Our studies of the direct affect of testosterone on the individual cancer cells will be greatly aided by further improvement in our cytological technics. Although we have been making these studies for some time, attempting to interpret the changes in cell content of phosphatase, nucleic acid, steroids and lipase, at least in our experience there is still much to be learned; and great improvements to be made in the technics before this histological method gives us the aid we need to interpret correctly the influence of the hormone on the individual cell. This method may eventually reveal the mechanism of testosterone action.

Although our group has had no experience with the study of radioactive phosphorus on breast cancer, as influenced by testosterone, it is obvious that a pursuit of this study might reveal important points which may help us interpret the action of testosterone in the individual cell.

Indirect Effect on Cancerous Tissue.—In the cases metastatic to bone, the great improvement evidenced by loss of pain and on x-ray films may partially be the direct effect on the cancerous lesion in the

bone; however the chief improvement seems to come from the sclerosis which takes place following testosterone therapy, not only in the local bone lesion but also in the osseous system as a whole. The improvement is due to the laying down of osteoblasts and the processes of bone repair and therefore represents an indirect reaction.

EFFECT ON METASTATIC LESIONS

Bone Metastasis; X-Ray Studies of Bone.—As the instances of improvement are much more striking and more common in bone metastasis than in soft tissue recurrence or metastasis, it may be of interest to study the appearance of bone during and following testosterone therapy.

In the average case of metastasis to bone, one notes the areas of absorption and destruction as holes in the pelvis, femora, spine, skull, humeri, and so on. In the case of the vertebrae, commonly there is a crushing and diminution in the width of the vertebrae affected. In a study of the bones of a large number of patients wi h bone metastasis, one is impressed with the lack of bone salts and density of the entire osseous system. Following testosterone therapy, one is again impressed with the contrasting new density of not only the destructive single lesions, but also the entire bony system. It gives one the impression of a much more rugged and strong bony system.

Case I.—R. C. H., married, aged 47, three years before had had a radical mastectomy which was followed two and one-half years later by widespread metastasis to thoracic and lumbar vertebrae, pelvis and femora. One was impressed with the appearance of lack of bone salts in the skeletal x-rays. The patient was fully incapacitated, being bedridden. In December 1946 a course of testosterone propionate was begun. Within a few weeks the patient was able to do some housework. Within eight weeks the x-rays showed a remarkable change throughout the entire bony system as evidenced by a marked increase in density of the bones and by local repair of the destructive lesions. Today, nine months after starting testosterone therapy, the patient is in excellent health, is leading her usual life, is camping, canoeing and dancing. We have her on a maintenance dose of 60 mg. of methyl testosterone daily.

She is an example of the effect of testosterone on the entire skeleton.

In the local area of destruction one first notes a surrounding zone of denser bone. This is followed by a filling in of the area with bone salts giving the appearance of callus. Even the bone trabeculae are frequently restored and visible. In cases in which there has been absorption of the rim of bone such as is frequent in the pelvic brim, a complete restoration of the original contour may take place. The following case will illustrate this:

Case II.—E. K., married, aged 47, had a radical mastectomy which was followed by multiple bone metastasis. X-ray therapy did not control the metastases, and especially painful was the bulky destruction of the upper half of the left humerus causing much loss of sleep. Testosterone therapy was commenced. Within

three weeks the pain had left the humerus and the heretofore immobile upper arm could now be moved without pain (Fig. 8). Remarkable improvement is noted also in the large destructive lesion of the right iliac crest where the contour of the pelvis was restored within a three month period (Fig. 9).

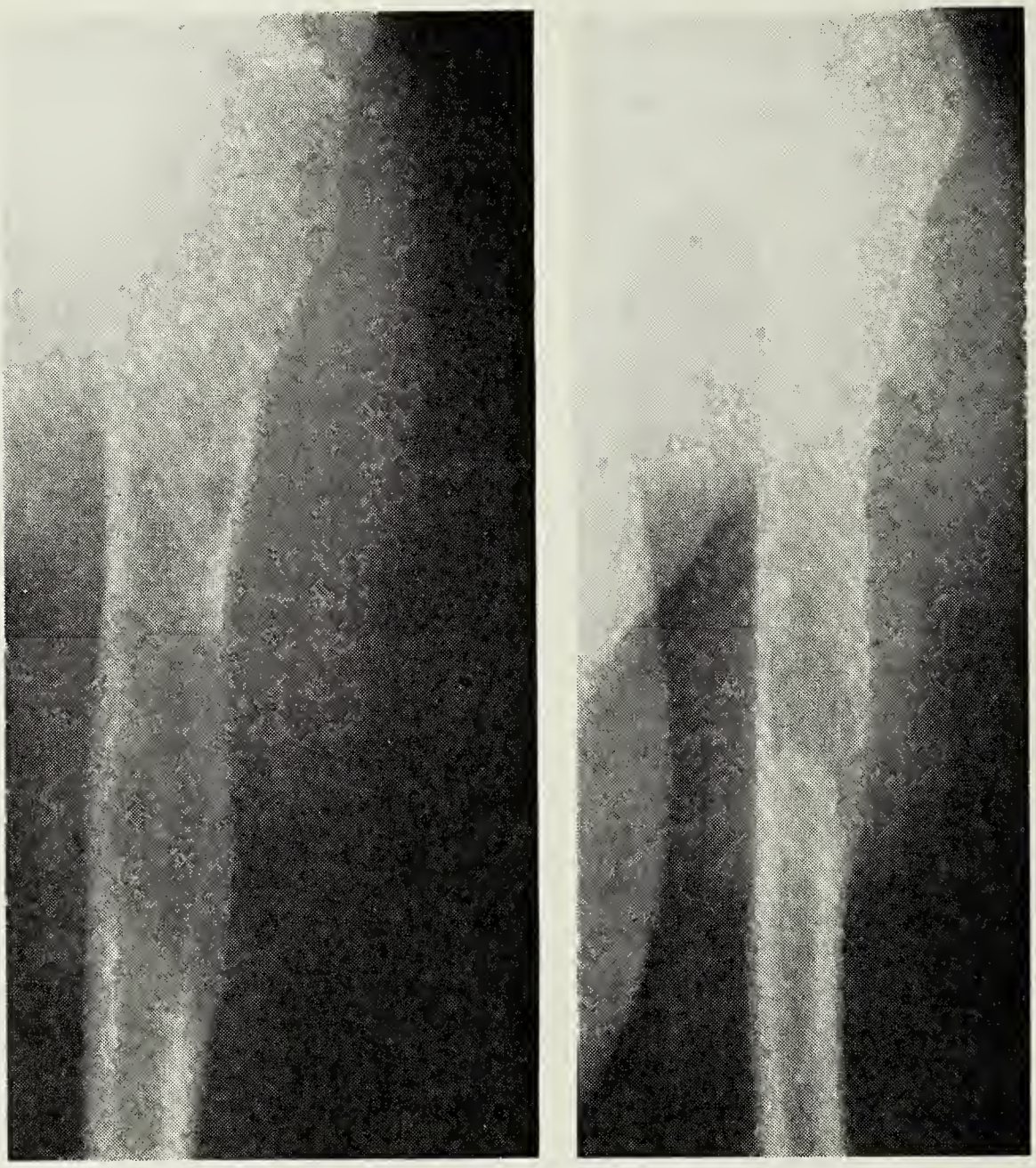
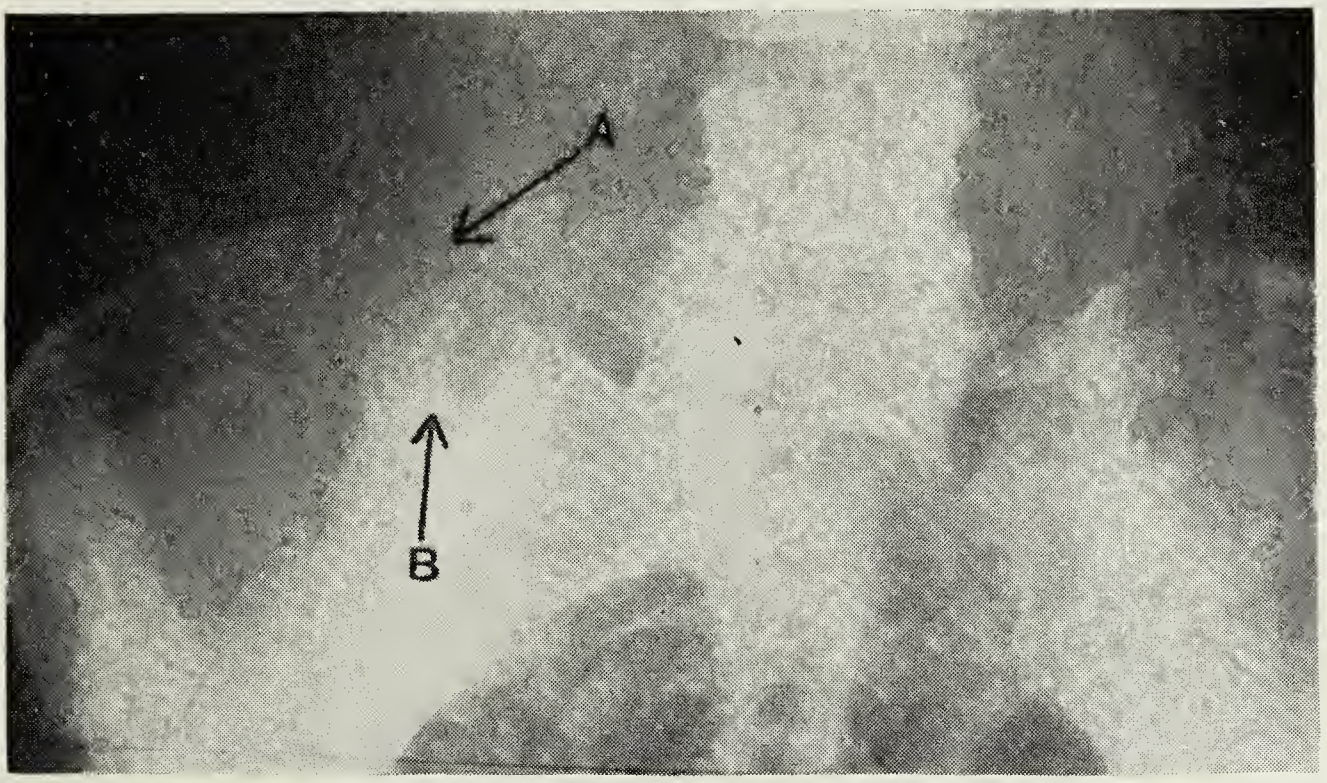


Fig. 8 (Case II).—*Left,* Left humerus on October 2, 1947 before testosterone therapy, showing destruction extending and including head of bone down to the lower half. Much of the cortex is destroyed together with massive destruction of the medulla. Intense pain on motion. Fracture imminent. *Right,* July 16, 1947, following testosterone therapy, showing great increase in density of upper half. The head and upper third are nearly restored. The cortex is much thicker and denser. No pain on motion.

Although local lesions in bone may undergo complete repair as far as one can tell by x-ray studies, unfortunately it is possible—and it happens frequently—that some other bony lesion, while under the same influence which healed one bone lesion, may continue to increase and apparently not be influenced as the other lesion was. An example of this is Case 4, D. F., *Annals of Surgery,*[2] in which the only lesion discernable when the patient came to us in March 1945 was the destruction of the left ala of the sacrum. Under testosterone propionate therapy the ala regenerated and again became dense bone

which bore her heavy weight without pain for a period of about one and a half years. During the latter part of this time she developed a new small bony lesion in the right pubic bone. This lesion developed



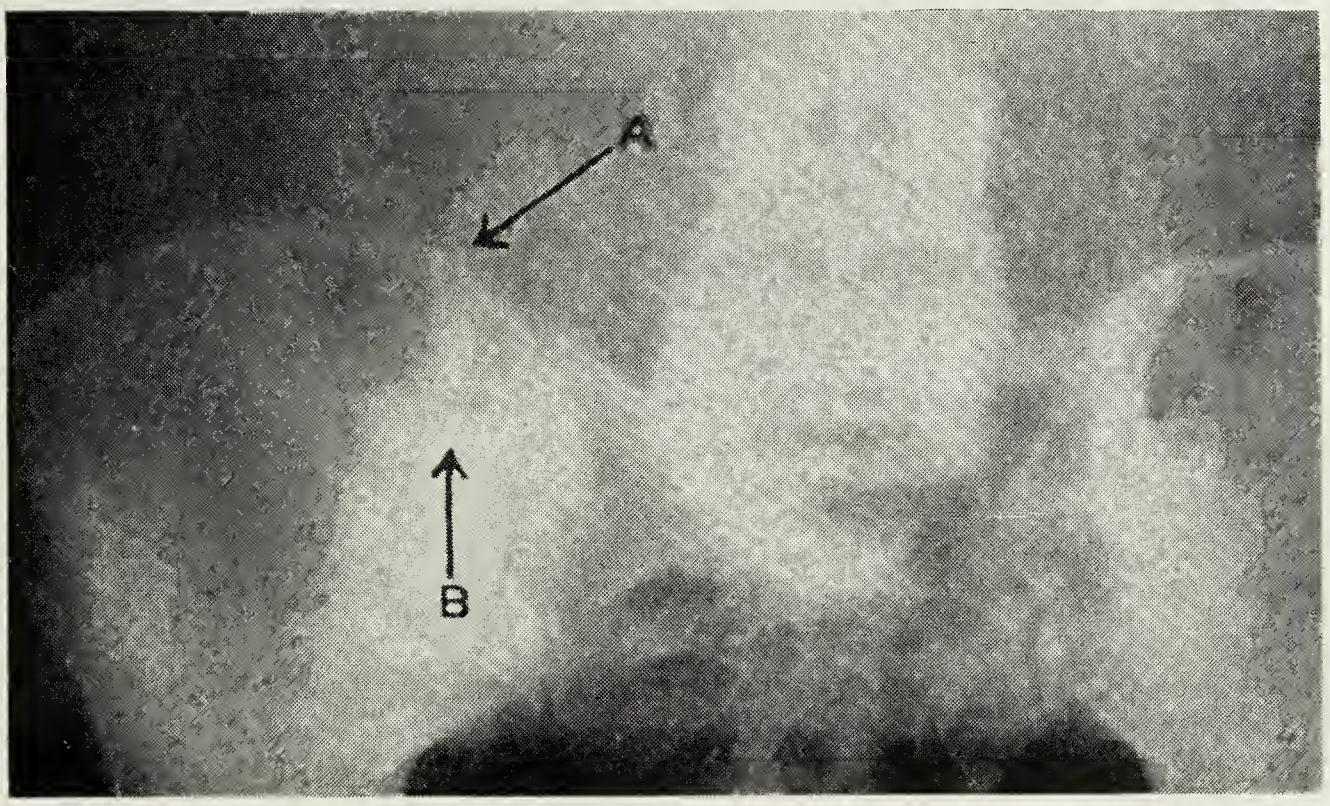


Fig. 9 (Case II).—*Upper,* Right pelvis on March 2, 1947 before testesterone therapy, showing massive destruction with loss of contour including the brim. *Lower,* June 16, 1947, three months after testosterone therapy, showing some filling in and regeneration of the area of destruction, together with restoration of the pelvic brim. The column at *B* is much widened and more dense; and extends to the very brim in contrast to upper figure where the column is shorter and much narrower.

further in spite of testosterone therapy. This is a good example of both the effectiveness of the ineffectiveness of testosterone therapy. The photograph (Fig. 10) shows the appearance of this patient in perfect general health exactly two years after the start of her testos-

terone in March 1945. However, shortly after the ending of the two year period she began to deteriorate from multiple bone lesions which had not been favorably affected like the original bone area of destruction in the sacral ala.

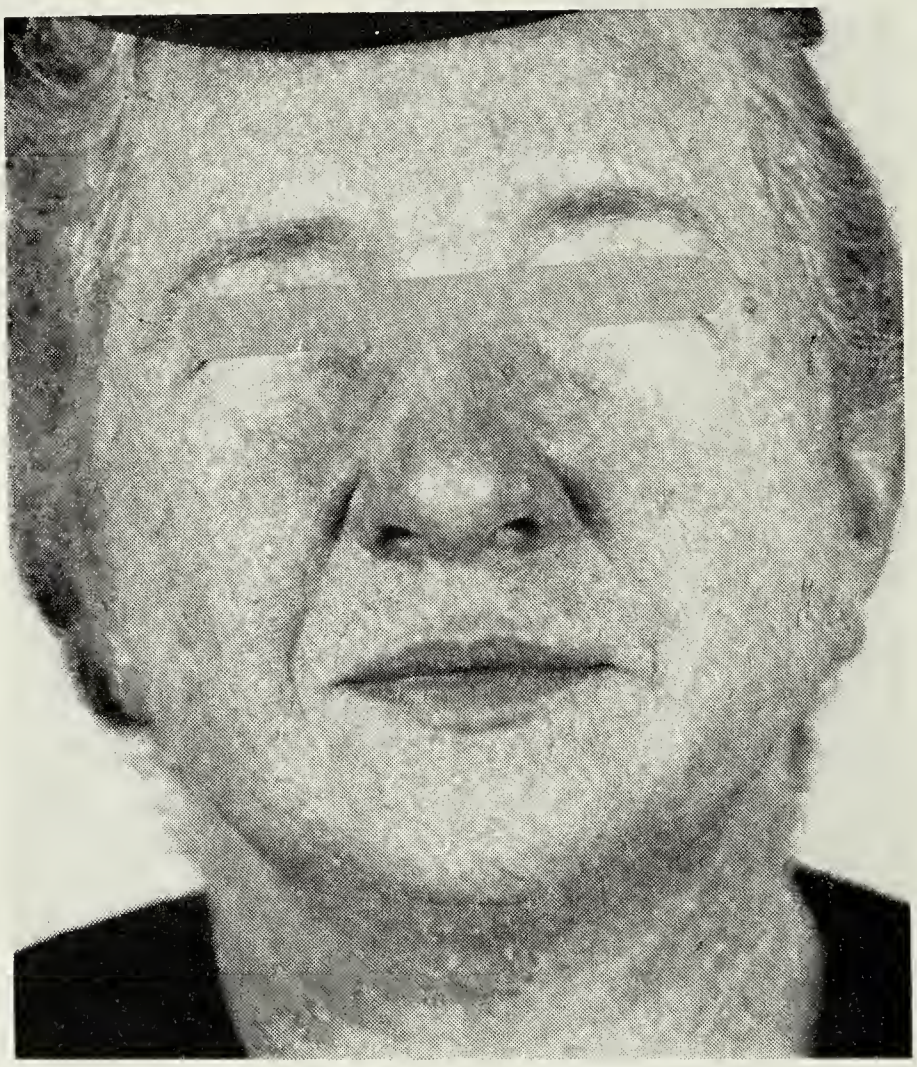


Fig. 10.—D. F. in March, 1947, showing the general appearance of good health exactly two years after testosterone therapy was started for the incapacitating destruction of the left ala of the sacrum.

Another instance of bone involvement in which the patient has survived for a period of over two years is the following:

Case III.—S. W., married, aged 56, came to me from Kentucky in June 1945. She had had a left radical mastectomy in June 1943 by Dr. Wm. A. Fisher of Johns Hopkins. Her last period was seven years ago. She had never been pregnant. She was a thin cachectic woman weighing 84 pounds, who complained of pain over the thoracic and lumbar spine, and tenderness over the entire skull. As she was entirely too ill to withstand a course of x-ray therapy she was sent home with instructions to have her physician telephone me. At the time, the x-ray report was the following: "Films of the skull: There are areas of cancer metastases to the vault, varying in size from a few millimeters to one area involving the entire frontoparietal region (Fig. 11). Areas of cancer involvement of bone are seen again at D3, 5, 8 and L3; probably also at the lower margin of the left sacroiliac joint; and the glenoid on the left. There are mild compression fractures of the dorsal vertebrae involved with slight compression of D8."

I instructed her physician to start giving 100 mg. of testosterone propionate three times weekly, which he did for a period of nine weeks. The patient developed the usual virilizing symptoms of hoarseness of voice and hair on the face.

As she was not within my immediate control, we did not have a blood calcium or alkaline phosphatase determination.

I quote from her letter to me three months later. "After lying in bed too weak to move—delirious sometimes—unable to eat, at long last I started to get better after we started the hormone shots. From a shadow of myself (about 80 pounds) I gained 16 pounds in ten days! In a few weeks I was doing my housework and running in high gear! . . . I sleep well—have a splendid appetite and my weight is about normal."

During the two years since the beginning of her testosterone therapy many of the areas of destruction in the skull regenerated with good bone. The outer table of the skull which was destroyed has regenerated (Fig. 12). The tenderness due

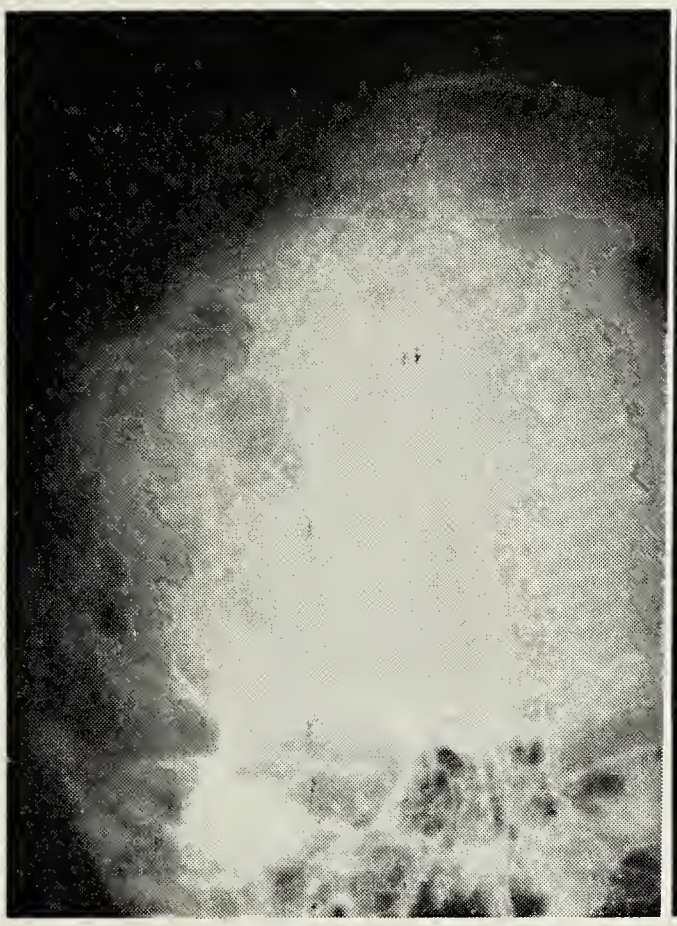


Fig. 11.

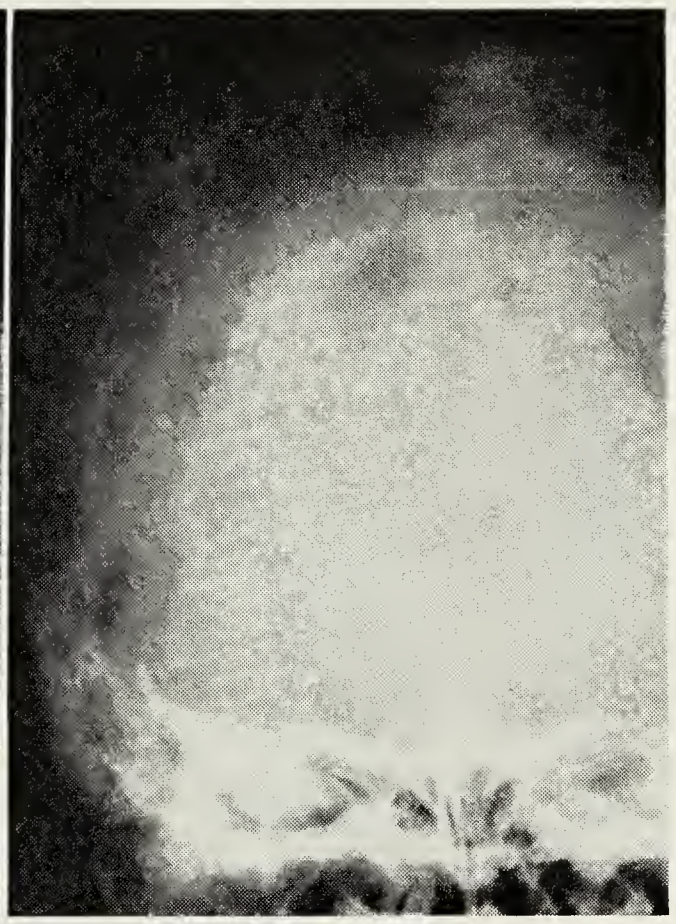


Fig. 12.

Fig. 11 (Case III).—Before beginning testosterone therapy, showing the multiple areas of destruction of the vault, and frontal bone and the complete absence of the outer table of the right skull. It was painful for the patient to lay her head on the pillow due to the tenderness of the scalp over the destroyed outer table of skull.

Fig. 12 (Case III).—Following first course of testosterone therapy (3000 mg.) showing a filling in of many of the smaller areas of destruction of the frontal bone, a regeneration and partial filling in of the larger areas together with a regeneration of the outer table of the skull.

to the skull destruction was especially bothersome to the patient when she lay her head on a pillow. This completely disappeared. On October 2, 1946 there was recalcification of the metastatic area in the left glenoid. No new areas of metastasis are visualized. Conclusions: "Cancer metastasis to bone, osteolytic type, showing interval density in some of the areas described."

On June 18, 1947, films of the skull, pelvis and lateral spine were obtained. "The previously described widespread cancer metastasis in the skull vault has increased in the interval. The appearance is mixed productive and destructive, the latter predominating. Previously described areas of cancer involvement in the vertebrae, with compression fracture, are essentially unaltered in the interval. Further changes are seen however in L4 and there has been mild interval extension of

cancer metastases in the pelvic area. New areas of metastases have appeared in the upper femora particularly in the neck area."

During 1946 this patient had a course of testosterone therapy of 50 mg. daily for thirty-one days followed by improvement. During the last months of 1946 the pain in the spine returned, her weight went down to 81 pounds, and she was in bed for eight weeks. Testosterone therapy was again started, the patient receiving 100 mg. three times a week for eight weeks. The back pain improved and the patient gained 17 pounds in weight, reaching 102 pounds.

This remarkable patient was seen by me in June 1947 (Fig. 13), exactly two years after she first came weighing 84 pounds., cachectic and with widespread

Fig. 13 (Case III).—General appearance of good health in the patient in June, 1947, exactly two years after her first appearance when she came with advanced skull, thoracic and lumbar spine involvement, together with pelvic, femur and scapula metastases.

involvement of bones. In June 1947 she slept well, had a good appetite, weighed 100 pounds, and was free from pain and full of vivacity and health.

Since this time I have heard rumors that the patient had a "stroke" which might possibly be interpreted as the result of an extension from the skull into the brain substance. However, I am not sure of the latter facts.

Had I been able to control this case by frequent observations, instead of the patient deciding on the indications for medication, it is possible that there might be a different outcome. She would call me only when she felt ill; and there was, after the first complete dosage, only intermittent testosterone attacks on the disease. As one looks backward it would seem that she should have been placed on a maintenance dose which possibly might have held the disease in check more consistently.

The above two cases are remarkable as evidencing that we now have an agent capable of prolonging life with the patient in fairly good condition for a two year period at least. If we had a more exact knowledge of medication with the hormones, it might be possible to further prolong palliation. This information will eventually come with greater experience.

We have never observed a patient with such widespread metastasis who survived two years in such a healthy general condition under any other form of therapy. Metastasis was too widespread for successful therapy by x-rays or radium.

In this consideration of bone pathology it is of some interest to note that, in a case of marked noncancerous osteoporosis with fractured hip and ribs, treatment with testosterone propionate resulted in a denser bony system within a two month period, accompanied by a gain in weight of 10 pounds within three weeks.

In a consideration of the intense pain and disability which accompanies bone metastasis, it is difficult to explain that there can be this complete loss of pain following testosterone therapy even when the crushing of one or more vertebrae still persists, and when the mechanics of the narrowed vertebrae pressing on the cord or intercostal nerves still exists. This, however, repeatedly happens. The relief of pain usually commences after about two to three weeks of hormone medication.

Soft Tissue Metastasis.—We have attempted to describe rather fully the changes which take place in bone metastasis. Although we are disappointed at the rarity of improvement in cases of soft tissue recurrence and metastasis, the occasional case is most striking in its improvement.

Abdominal Metastasis.—Results in the following case of metastasis from the breast to the abdomen have been most gratifying under testosterone therapy.

Case IV.—A. D., married, aged 41, came to me July 31, 1946 with a large lump in the right breast and rather bulky right axillary metastases. She had three children. She still menstruated regularly every twenty-eight days. On August 12, 1946 a radical mastectomy was done. Pathological report was: "Infiltrating duct carcinoma, grade III, metastatic to nodes from the base to the apex (all levels)." This was a rather advanced or borderline case for operation. The operation was followed by postoperative x-ray therapy over the axilla and supraclavicular areas.

On December 5, 1946 the patient's hemoglobin was 71 per cent and sedimentation rate 81 per minute; she complained of abdominal discomfort. By February 2, 1947 there was marked abdominal ascites. She was admitted to Memorial Hospital for paracentesis. Five liters of blood-tinged fluid containing microscopically proven cancer cells were removed. After paracentesis abdominalis, tender masses were palpable within the abdomen especially in the suprapubic region, also a 20 by 15 by 10 cm. pelvic mass. On February 19, 1947 a course of testosterone propionate injections was begun. On March 18, 1947, although she had looked desperately ill previously, she was improved and there was less abdominal fluid. We were never able to palpate an enlarged liver. During the weeks past she had

been tapped several times. By April 17, 1947 the patient had gained 7 pounds and no fluid was present. By May 16, 1947 she had gained 15 pounds and no fluid was present. She felt well. The testosterone injections were terminated on July 24, 1947, the patient having taken them since February 1947, during which period she gained a total of 20 pounds. Her voice is husky. No fluid is present. She was started on methyl testosterone, 30 mg. daily.

If one tries to explain this remarkable case, he might conclude that we were dealing with an advanced case of breast cancer metastatic to the peritoneum, in which five months of testosterone therapy had a profound effect on peritoneal metastases. As the patient received no x-ray therapy over the abdomen, it would seem that the action of the hormone was a direct one on the abdominal cancer cells.

Chest Metastasis.—We have used testosterone in approximately twenty cases of chest metastasis. It has been a disappointing experience. With the exception of about three, one of which was reported in *Clinical Endocrinology*,[5] there has been little to encourage us in this group of cases of soft tissue metastasis. It is possible that, after lung involvement once takes place, the course is rapidly downhill, and the patient may not have enough time to get the proper amount of the hormone to be effective.

Liver Metastasis.—We have also employed testosterone in about fifteen cases of liver metastasis. In three cases the liver seemed to diminish in size, but our impressions are still somewhat vague as to its value in this organ. We are doing routine liver function and kidney function tests in all cases of suspected liver metastasis. In massive liver metastasis, the alkaline phosphatase may go as high as 50 units or more per 100 cc.

In dealing with soft tissue metastasis, the proportion of cases which are strikingly improved is so small that it places one on his guard against too much optimism and inaccurate interpretation.

MISCELLANEOUS FACTORS

Dosage.—In our cases at present we are employing 100 mg. of testosterone propionate by intramuscular injection three times a week for ten weeks, making a total of 3000 mg. Following this, a maintenance dose of 40 to 60 mg. daily of methyl testosterone by mouth is given for eight weeks. The proper amount of methyl testosterone to maintain amenorrhea is not yet determined but, when it is, we probably should keep the patient on this dose indefinitely to inhibit estrogen action.

Vaginal Smears.—In addition to the clinical picture of improvement which is usually so definite in bone metastasis, frequent studies of vaginal smears (Papanicolaou technic), have been found by Dr. Mellors of our group to be of inestimable value in guiding us in our determinations as to need for further therapy. Under the influence of testosterone therapy the vaginal smear soon changes into a basophilic

picture. By a study of the smears one can even determine if the patient is actually receiving the hormone. It is a helpful guide in studies of the effects of both the estrogen and the androgens.

Weight.—Under testosterone therapy there is usually a gain in weight. It is due to two causes, namely nitrogen retention and improvement in general health. Most patients feel better while under testosterone therapy. If they have had loss of sleep from painful metastases the relief from pain may be a factor in the weight gain.

Chemistry.—Many chemical studies are indicated in this new field, if we are to arrive quickly at a more exact knowledge than is obtainable by the slower method of clinical observation by trial and error. Our studies at present in any given case comprise the routine blood and urine examinations; calcium, phosphorous and phototase determinations; liver and kidney function; and in the occasional case, determination of the fractionated 17-ketosteroids. We hope soon to have a bed for metabolic studies where we can establish the changes in protein metabolism, electrolyte equilibrium, nitrogen balance, creatinine, uric acid excretion, blood urea, and the albumin-globulin ratio. We hope to further the study by determination of the urinary gonadotropic hormones.

For nearly a year we have been making cytochemical studies of tissues, both normal and neoplastic, removed from the breast at operation.

We have noted that, during clinical improvement in our cases of bone metastasis under androgen therapy, the blood calcium usually returned from its abnormal high of 12 to 15 mg. to its normal range of 8 to 10 mg. per 100 cc.; and as an evidence of bone repair and regeneration the alkaline phosphatase rises from its normal of 3 to 5 units to, at times, as high as 15 to 17 units per 100 cc.

SUMMARY

1. An abstract of the literature of the clinical use of androgens in human breast cancer is included.

2. It is to be emphasized that the work in the field of androgen therapy in cancer of the human breast is so new that we have not had opportunity to establish the exact dosage to accomplish the palliation desired. We have established, however that heavy dosage *only*, gives palliation which is more than temporary.

3. We have presented two cases of bone metastases in which what may be considered successful palliation has been obtained for over two years.

4. Aside from the virilizing effects of the androgen, and those rare cases with an established high level of blood calcium in which the testosterone therapy appeared to contribute to a general malaise and sickness, there are no contraindications to the use of testosterone in advanced cases of breast cancer.

5. On the other hand it is common, in cases with metastasis to bone, to obtain under androgen therapy relief of pain, removal of disability, increased appetite, gain in weight, ability to sleep without narcotics, delay in the normal growth processes of metastatic cancer, and a feeling of well-being.

6. In an exact study of a well controlled series of cases of breast cancer, it may possibly be proved that a continued regimen of testosterone, sufficient to suppress estrogenic influence, may be indicated. This remains to be established.

7. The influence of testosterone on growth processes of mammary carcinoma is so profound and so striking, even though so frequently disappointing, that clinical and metabolic studies should be pursued by investigators with the greatest vigor.

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INFERTILITY OR STERILITY IN THE FEMALE

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The childless family is an important medical and sociological problem. Few married women prefer to go through life without offspring. Motherhood still has almost universal appeal. It has been estimated that somewhere between 15 and 20 per cent of our marriages are childless involuntarily. These disappointed women trudge from one physician to another in the hope that some miracle of science can bring them happiness.

The study of infertility in the female has made great strides in recent years. It is possible to determine the cause of a failure of conception in most cases. Although it is not possible to remedy the defects in all instances, at least a third of all sterile couples who are subjected to a complete sterility work-up ultimately have children. In fact, the various diagnostic procedures necessary to determine the cause for the lack of fertility are in themselves therapeutic as well as diagnostic. Thus, a complete and careful diagnostic survey is of the utmost importance.

How long should a couple try to have a family before it seeks medical aid? Although the period of infertility is of important prognostic value, no arbitrary time can be selected following which the couple can consider itself sterile. If a patient consults a physician with the complaint of "failure to conceive" she is entitled to a complete sterility study regardless of how long she has tried to have children. Much more can be done in young women than in women nearing the end of the reproductive years. Rubin has recently suggested that couples who use contraceptives should have sterility studies, for many of these couples could not have conceived in any event.

Contraception for child spacing does not in itself decrease the fertility of the woman. A good many patients do not desire children during the first year or two of married life. They wish to enjoy the freedom and newfound happiness unencumbered by responsibilities. Perhaps they wish to make their economic position more secure by working so that their children may benefit from their increased resources. Too long a delay in raising a family may well decrease fertility. The early twenties are the years of highest fertility. The thirties show an increasing decline and there is a rapid ebb after forty. Thus youth is the best ally of motherhood.

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The physician should encourage the examination of the sterile couple rather than the examination of the wife. It is still too common practice to regard the woman as the sole responsible agent for the failure to conceive. Nothing is further from the truth. All statistics including ours at the Chicago Lying-in Hospital indicate that, in at least one-third of the sterile couples examined, the husband is responsible for the failure of conception. Furthermore, in another third of our group the husband is an important contributing factor in the low fertility of the couple. The husband can be referred to a urologist, if necessary, but no sterility study is complete without a complete work-up of both members of the family.

ORGANIC FACTORS WHICH INFLUENCE FERTILITY

Congenital Anomalies.—Normal anatomic structures with normal physiologic function are necessary for reproduction. Fortunately, portions of the reproductive organs have been duplicated so that malformation or disease may destroy certain segments and pregnancy and delivery of a normal infant still be possible. The fallopian tubes, the uterus and vagina are all formed embryologically by a fusion of the müllerian ducts. The uppermost portion of these ducts do not fuse, allowing for the formation of two fallopian tubes, the middle segments merge to produce the entire uterus and the lowermost portion the vagina. Numerous variations from the normal pattern are found and they represent a lack of normal embryologic development. The uterus may be arcuate in character; the corpus may consist of two separate horns, bicornate; or there may be a complete lack of fusion of the müllerian ducts at this level, resulting in two complete uteri (Fig. 14). This failure of embryologic fusion may extend their entire lengths, giving rise to two vaginal lumens as well, and a complete duplication of the reproductive tract will result. These congenital anomalies influence fertility to some degree but they cause sterility rarely. There are unusual instances in which one segment of the reproductive tract has failed to develop, thereby interfering with continuity of the passageway. There may be a complete absence of the vagina, the uterus, or both. These major defects make pregnancy impossible.

Infection.—Disease may alter the normal state of the reproductive organs and interfere with normal fertility. Infection is the most common and the most serious complication. The infection may be gonorrheal in origin or it may be the result of an abortion; more rarely it may follow childbirth. These infections involve the fallopian tubes, interfering with the patency of their lumens and grossly altering tubal function, so that the oviduct is no longer suitable for transport of the fertilized ovum. Infections of the fallopian tubes involve both structures most often. The residual damage varies with the virulence of the organism and the resistance of the tissues.

In about 5 to 10 per cent of infections of the upper genital tract tubercle bacilli are the causative agents. Tuberculosis of the genital organs most often involves the fallopian tubes and the endometrium of the uterus, and the disease is usually secondary to some focus elsewhere, such as the lungs or the peritoneal cavity. Fertility is almost invariably destroyed.

Infections of the lower genital tract such as trichomoniasis, monilia vaginitis, and nonspecific infections are no barrier to conception but they may reduce fertility. Thus, an endocervicitis is likely to alter the

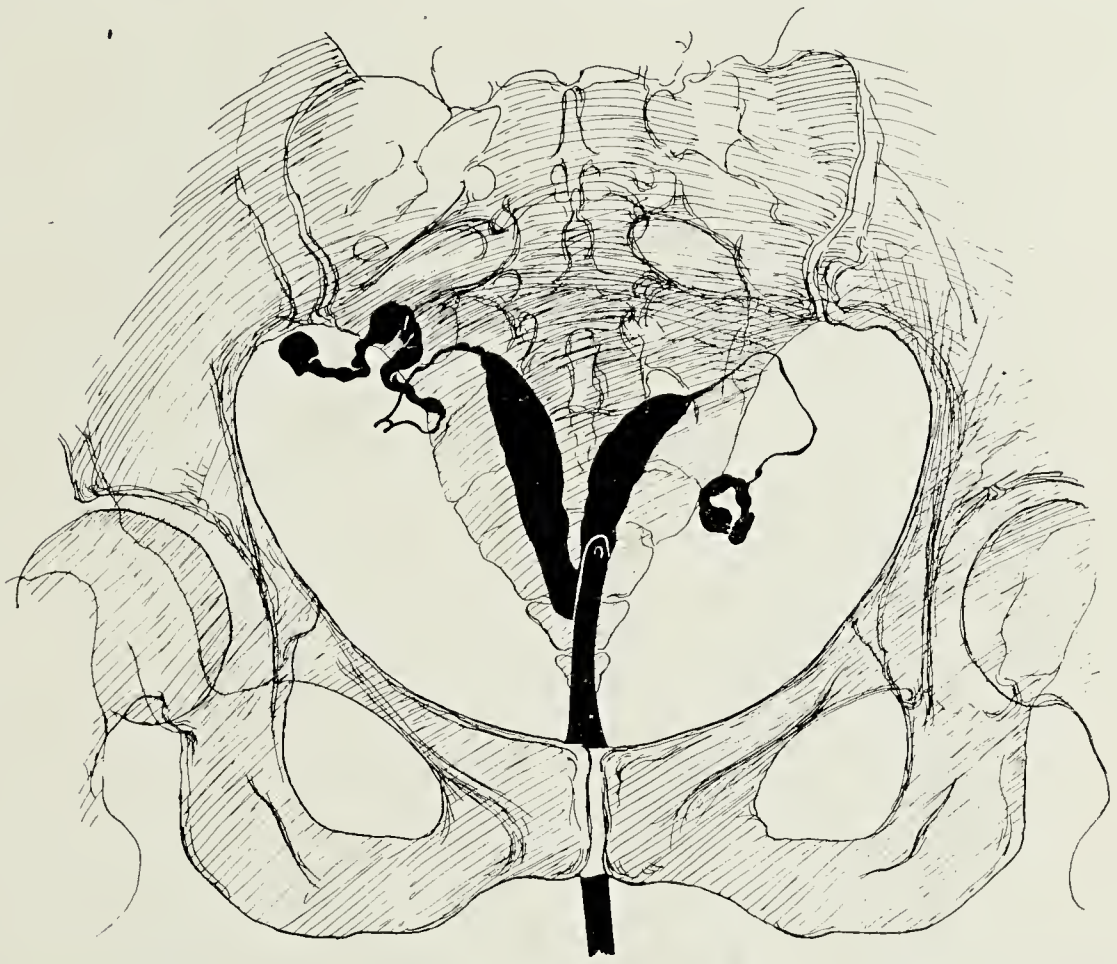


Fig. 14.—A salpingograph showing a complete lack of fusion of the müllerian ducts and the uterus completely duplicated.

character of the cervical mucus to such an extent as to interfere with the normal passage of spermatozoa through this zone. Pus cells in the mucus are inimical to the survival of spermatozoa.

Neoplasms.—Neoplasms of the reproductive organs may reduce fertility but they cause sterility rarely. Fibroid tumors of the uterus are a common complication in many women who seek medical aid for sterility. The relationship between fibroid tumors and infertility is not understood clearly. It is not likely that the tumors in themselves interfere with fertility seriously. It is more likely some predisposing cause is responsible for the reduced fertility and the neoplasms. Fibroid tumors are very much more common in women who have never had children than in women who have had families.

Ovarian Tumors.—Ovarian cysts and new growths do not interfere with fertility except in the rare instances in which they produce hormonal substances. The small cysts which are the result of ovarian

malfunction need treatment rarely for they may be transitory and slowly disappear. True neoplasms should be removed because of the hazard of malignancy.

Uterine Retrodisplacements.—The normalcy of the reproductive organs includes their relationship to one another. Any distortion in this relationship may theoretically reduce the fertility of the individual. Malpositions of the uterus have been indicted as barriers to conception. In most instances the position of the uterus is of no great importance. Adherent retrodisplacements of the uterus, particularly if these are associated with retrodisplacements of the adnexa, may inter-

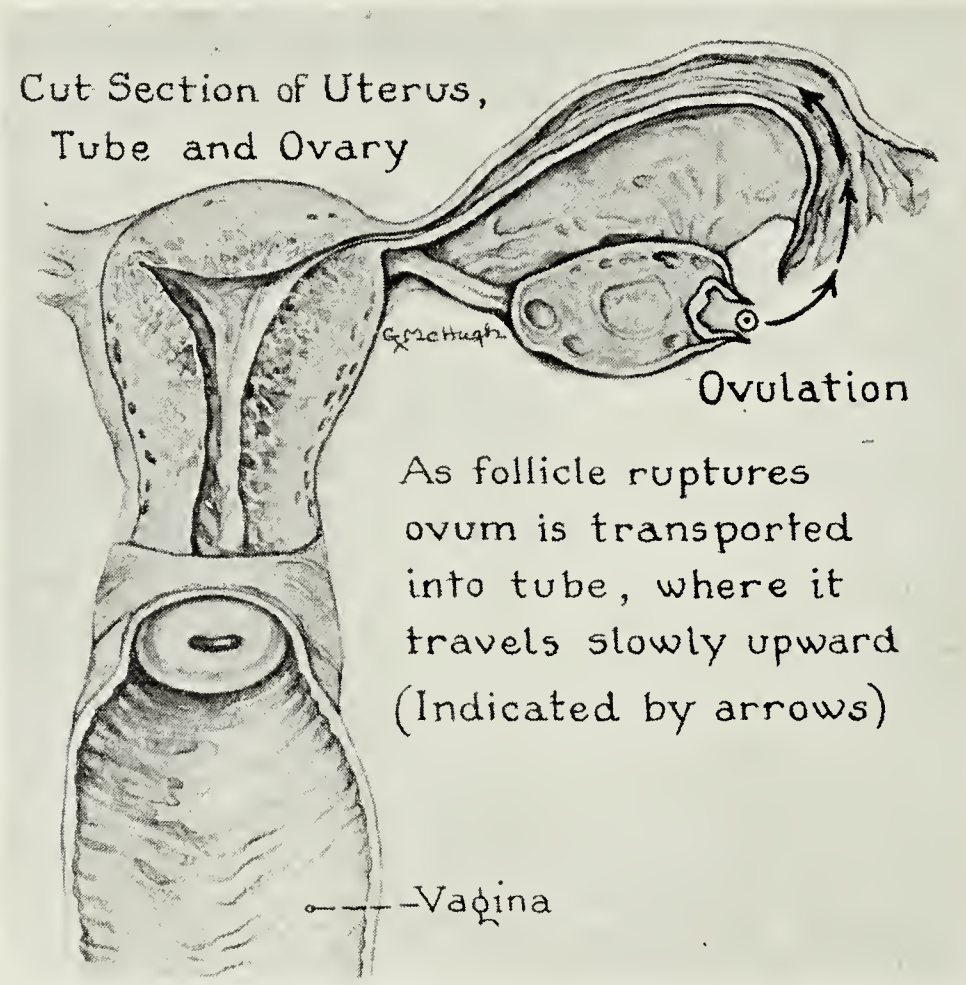


Fig. 15.—(*For legend see facing page.*)

fere with the normal passage of spermatozoa upwards to meet the ovum in the fallopian tube. It is true that many clinicians have replaced a uterus temporarily by means of a pessary or more permanently by surgery and the patient has conceived rather promptly. However, it is equally true that in about 15 per cent of normally fertile women the uterus remains in a retrodisplaced position.

PHYSIOLOGY OF THE REPRODUCTIVE ORGANS

The structure of the reproductive organs may be normal, but they must function normally if conception and normal pregnancy are to occur. The ovary must produce ripe follicles with mature eggs at periodic intervals. The follicle must rupture and discharge the mature ovum. The ovum must find its way into the fallopian tube by an ingenious mechanism developed for its reception and transport down

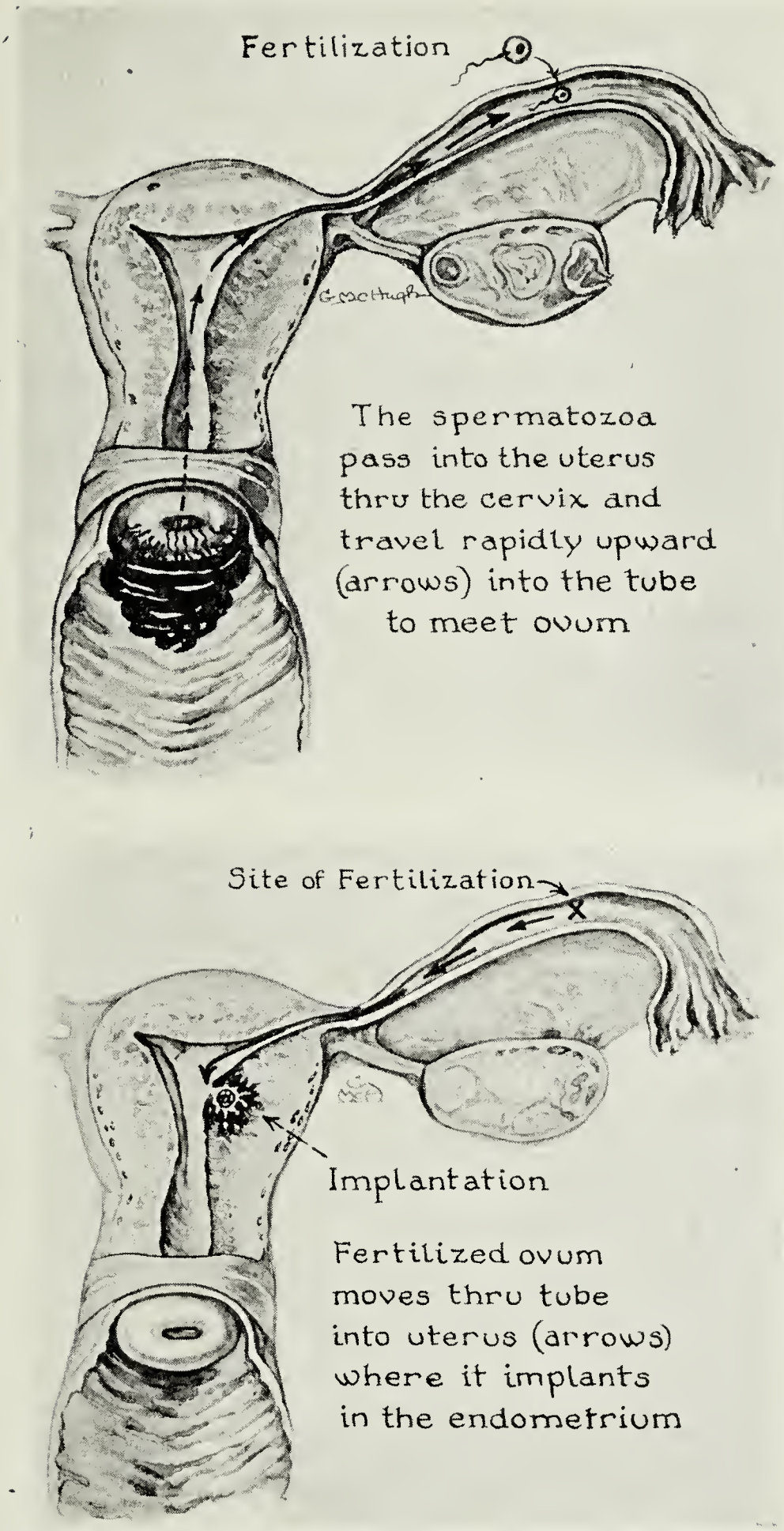

Fertilization
The spermatozoa pass into the uterus thru the cervix and travel rapidly upward (arrows) into the tube to meet ovum
Site of Fertilization
Implantation
Fertilized ovum moves thru tube into uterus (arrows) where it implants in the endometrium

Fig. 15 (*Continued*).—Diagrammatic illustration of ovulation, fertilization and the transportation of the fertilized ovum into the uterus where implantation takes place.

the tube. Fertilization occurs in the tube following which the peristaltic action of the muscular wall moves the fertilized ovum into the uterine cavity. The endometrium in the uterus has reached a state of development suitable for the attachment and implantation of the small vesicle by the time it has entered the uterine cavity.

The cyclical changes in the ovary and the uterus which make fertility possible are controlled by the glands of internal secretion. Under the influence of a hormone elaborated by the anterior lobe of the pituitary gland, follicle-stimulating gonadotrophin, primary follicles in the ovary develop and their ova mature. Periodically, about once a month in most women, under the stimulus of a second hormone from the anterior lobe of the hypophysis, luteinizing gonadotrophin, one and rarely two or more follicles are stimulated to a sudden spurt of growth. The ovum rapidly matures and the follicle ruptures, allowing the ovum to escape. This phenomenon is known as ovulation. The escaped ovum finds its way into the fallopian tube as a result of local currents, ciliary action or peristaltic activity of the tubal musculature. The ovum must be fertilized promptly, for it is not capable of fertilization after twelve to twenty-four hours.

Coitus must take place within twenty-four to thirty-six hours of ovulation. The lives of spermatozoa are longer than that of the ovum, and they, too, perish rapidly. The vaginal secretions are acid and usually destroy the spermatozoa in the vaginal lumen in three or four hours. The cervical mucus is highly favorable to the survival of the sperm cells. Normally, its consistency changes about the time of ovulation so that it becomes less viscid and more penetrable. This change in the character of the cervical mucus is an important feature of the reproductive cycle and is brought about by one of the ovarian hormones, progesterone. The cervical canal provides a haven for the spermatozoa from which they can travel upwards to meet the ovum in the fallopian tube. Disease of the endocervix is an important barrier to conception (Fig. 15).

The changes in the endometrium necessary for the reception and implantation of the fertilized ovum are under the control of the ovarian hormones. The developing graffian follicle in the ovary produces estrogenic hormone. This substance provokes the growth of the endometrium so that, about the time ovulation occurs, it has increased in thickness several times. The rapid maturation of the follicle, its rupture and the release of the ovum provide the second of the ovarian hormones, progesterone. The collapsed wall of the follicle undergoes rapid proliferation, and shortly a full-blown corpus luteum develops. The corpus luteum provides estrogens as well as progesterone. Under their combined influence the endometrium changes into the progestational state suitable for implantation. The glands become tortuous and full of secretion rich in glycogen. The stroma cells swell up and take on decidual characteristics. Increased vascularity provides for the marked activity of all the components of the mucosa (Fig. 16).

Progesterone has been called the pregnancy hormone for it is primarily concerned with reproduction. It will continue to exercise a vital role throughout the gestation, although the placenta ultimately takes

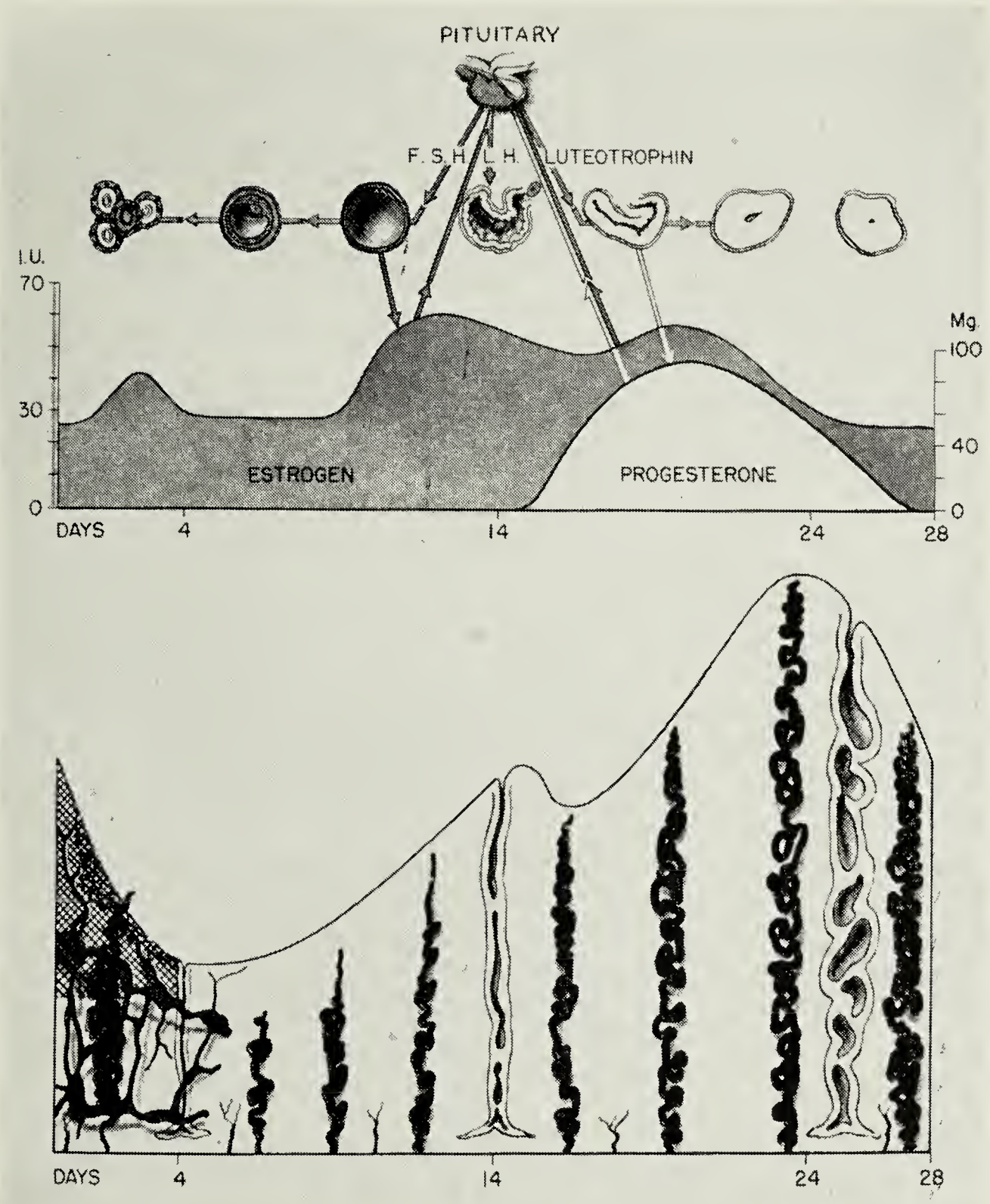


Fig. 16.—The diagram shows the endocrine relationship and endometrial growth changes in an average 28 day menstrual cycle. Under the influence of the follicle-stimulating hormone (F. S. H.) from the pituitary the follicle grows and the ovum matures. The introduction of the second pituitary gonadotrophin, the luteinizing hormone (L. H.), results in the rupture of the ripe follicle and the conversion of its wall into the corpus luteum.

The lower part of the figure represents the endometrial changes. Under the influence of the estrogenic hormone produced by the follicle the endometrium grows in thickness. Following ovulation the second ovarian hormone, progesterone, produced by the corpus luteum converts the endometrium into progestational phase so that implantation of the fertilized ovum can take place. (Markee, Progress in Gynecology, Grune & Stratton.)

over the production of this important substance from the corpus luteum.

In the event that the ovum is not fertilized, the preparation of the endometrium is unnecessary. The corpus luteum undergoes rapid retrogression. Progesterone production ceases, and the drop in the level of this hormone probably brings on menstruation. The menses are a destructive phenomenon designed to remove the unnecessary highly developed lining of the uterus.

This brief description of the function of the reproductive organs emphasizes the intricate mechanism involved in the normal fertility of the individual. The proper function of the glands of internal secretion as well as normal reproductive organs are necessary. Reproduction is dependent on a carefully timed mechanism recurring cyclically. Any abnormality in structure or function of the reproductive organs decreases the fertility or results in sterility.

STERILITY STUDY

Our sterility studies consist in evaluating organically and functionally the normalcy of the reproductive organs and their regulatory endocrine glands. Examination may uncover a condition which makes childbearing impossible or it may reveal a number of factors which tend to decrease the fertility of the individual. Often there are findings in both the male and female which combine to decrease the level of fertility of the couple below the threshold necessary for conception. Successful treatment will depend on correcting as many factors as possible which decrease the fertility of the husband and wife.

History.—A careful history may reveal pertinent information concerning the inability of the patient to conceive. Delayed puberty and adolescence may be indicative of ovarian failure. Abnormalities in the menstrual pattern may likewise point to the ovary and its regulatory glands of internal secretion as important factors. A history of pelvic infection or a criminal abortion may throw light on the cause of tubal disease, such as gross alterations in the tubes, obstructions in their lumens, or complete blockade. The results of previous examinations for sterility may often provide helpful data. A history of important medical complications may throw light on the status of the pelvic organs. The results from surgical procedures of all kinds, particularly when they have involved the pelvis, should be carefully explored in order to determine if organs or portions of them have been removed or grossly altered. The history of previous pregnancies in patients with secondary sterility may shed light on the present situation. It is well to point out that a careful history of the husband is equally important in a complete sterility study.

Physical Examination.—The physical examination should include a complete medical survey of the patient as well as her pelvis. It is important to know whether she has heart disease with which childbearing may be contraindicated. Active tuberculosis is likewise a contraindication to pregnancy until such time as the process has been

arrested. Pelvic inflammatory disease of unknown etiology may be identified as tuberculous in origin if some active focus outside the pelvis is discovered.

A careful pelvic examination will reveal deviations from the normal as well as evidences of disease. The character of the development of the external genitalia and the general physical habitus will throw light on the development of the reproductive organs. Evidences of pelvic infection may be apparent in the periurethral glands, Bartholin's glands or the urethra.

The cervix as an important part of the reproductive mechanism deserves special study. Note its location, shape, character of the external os and patency of the lumen. Erosions, lacerations, endocervicitis and strictures of the lumen may provide barriers to conception. The cervical mucus should be studied for consistency, the presence of pus cells and bacteria.

The corpus should be palpated, and its position, size, symmetry and mobility noted. The normal uterus may be retroverted, but it should be freely movable. A cervix that points toward the symphysis is usually found when the corpus is retrodisplaced. It is doubtful if the cul-de-sac pool of seminal fluid into which the cervix dips is a necessary accompaniment of high fertility. It is more than likely that the spermatozoa that could fertilize the ovum gain access to the cervical mucus directly during intercourse.

Normal adnexa are rarely palpated except in thin women. Enlarged, adherent and tender adnexa are the result of pelvic inflammation. They may restrict the free movement of the uterus and thereby become evident. Enlargements of the ovary as a result of cysts or neoplasms can be palpated adjacent to the uterus.

Hysterosalpingography.—Pelvic examination is the first step in an evaluation of the normalcy of the pelvic organs in the same way that an abdominal examination should precede the roentgenologic visualization of the gastrointestinal tract. Rubin's classic contribution in demonstrating patency of the reproductive tract opened a new chapter in the study of the sterility patient. He reasoned that for the spermatozoon to meet the ovum there must be a continuous passageway from the vagina into the peritoneal cavity. This continuity could be established by the passage of air or a gas through the cervix, uterus and fallopian tubes into the peritoneal cavity. Since this initial development opaque substances have been used in order to visualize the pelvic organs as well as to establish their patency. Both procedures, the use of a gas and roentgenological visualization, have their place in sterility studies and complement one another. At the initial examination it is desirable to use contrast medium to visualize the reproductive organs fluoroscopically and by means of x-rays to establish their condition and provide a permanent record. Subsequent examinations for patency should probably be limited to the passage

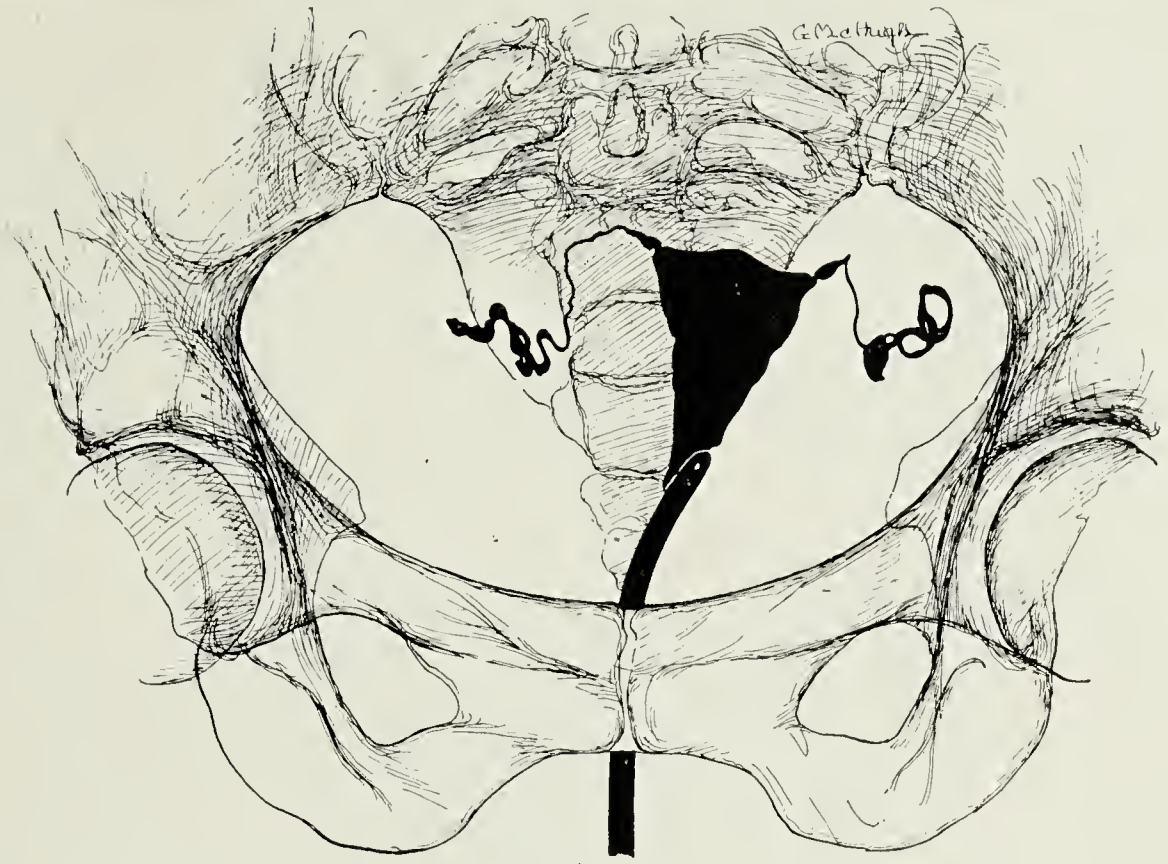
of gas through the tubes. Most contrast medias that are used are not absorbable, and repeated injections may produce tissue irritation.

Visualization of the reproductive organs and establishing the patency of the tubes can best be carried out the first few days after a menstrual period. It is well to inject the opaque medium under fluoroscopic control so that the filling of the uterus, the flow into the tubes and the spill can be seen. The cannula should be connected to a manometer so that the pressure under which the oil enters the uterus can be controlled accurately, and limited to 250 mm. mercury. Greater pressures are not safe. Roentgenograms should be taken as soon as the tubes are visualized, before too much spill has occurred. There are excellent mechanical devices by which air and contrast media can be injected under carefully controlled conditions. The Gynogauge can be used and a kymographic record of tubal activity obtained following which contrast media may be used to visualize the reproductive organs. On the completion of the examination the patient should rest for a short time, following which she can return home. She returns the next day for a second filming to provide more evidence of tubal patency.

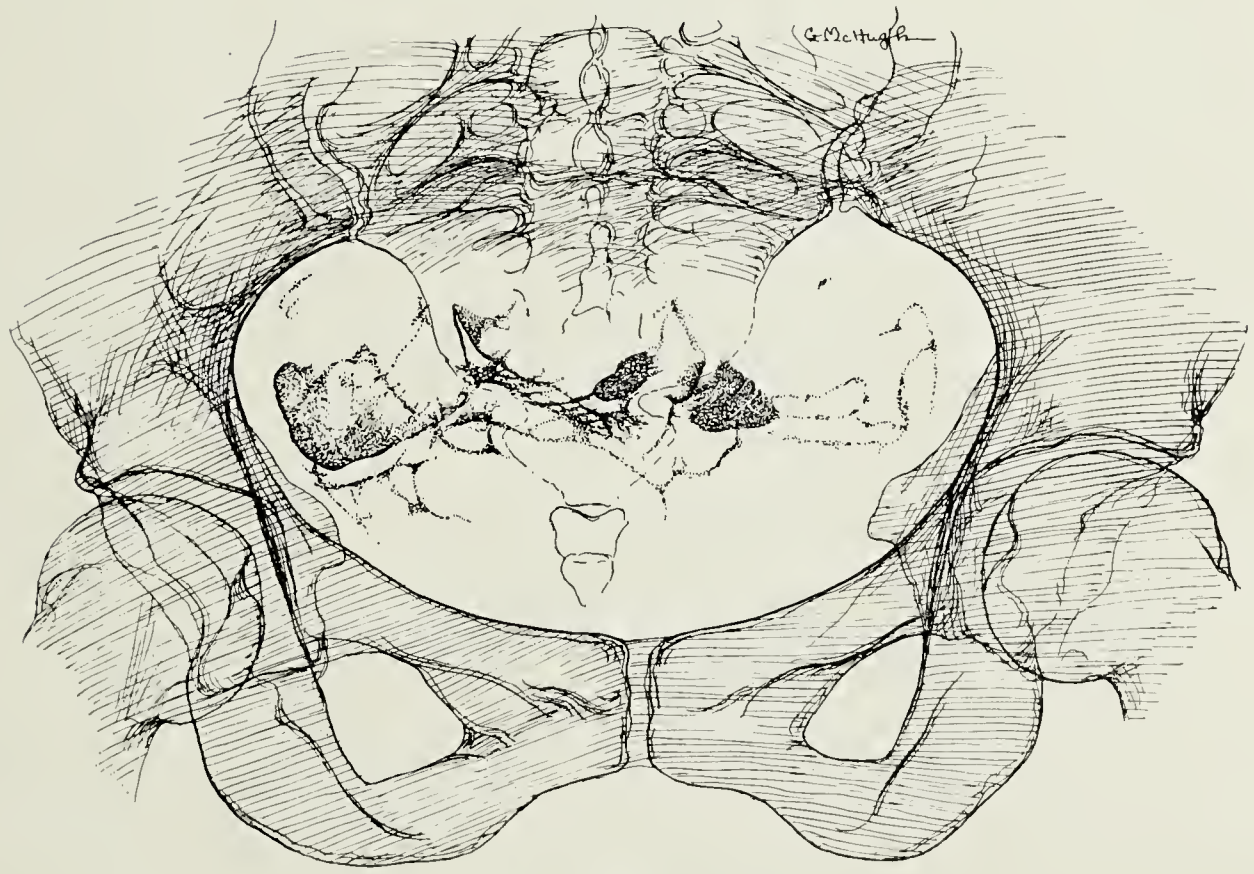
The visualization of the reproductive organs can be carried out with little risk if patients are selected properly. Recent pelvic inflammatory disease is a distinct contraindication to the procedure. Endocervical infections and infections of the lower genital tract should be eliminated prior to any attempts at salpingography. Care should be exercised to prevent the introduction of infection from the outside as well as lighting up an existing latent infection. Oil may be injected into the veins in the wall of the uterus. If a network of vessels appear fluoroscopically, no more oil should be injected. There is little danger of oil emboli because of the limited amount which will escape into the circulation. The appearance of oil in vessels along the fallopian tubes may lead to an error in the interpretation of the hysterosalpingograph.

If salpingography is carried out with care, the uterine cavity is beautifully visualized. The size and the symmetry of the uterus may be apparent as well as its position in the pelvis. Opacities in the uterine shadow may be produced by neoplasms or polyps. When the fallopian tubes are visible, much information can be obtained concerning their normalcy. They may be elongated, adherent to pelvic structures or grossly enlarged. The lumen may vary in size and regularity instead of slowly increasing in diameter from cornua to ostium. The tubal lumen may not fill throughout its length, indicative of blockade at the cornua, or the entire tube may fill but no spill occur from the ostium. Hydrosalpinx formation may be evident in the droplet formation of the retained oil. The twenty-four hour plates should show a characteristic smear of the oil among the pelvic viscera if the tubes are patent. Restricted smearing or pocketed accumulations of oil are

indicative of localized adhesions. Tuberculosis of the tubes may produce very long tortuous structures which may be partially patent.



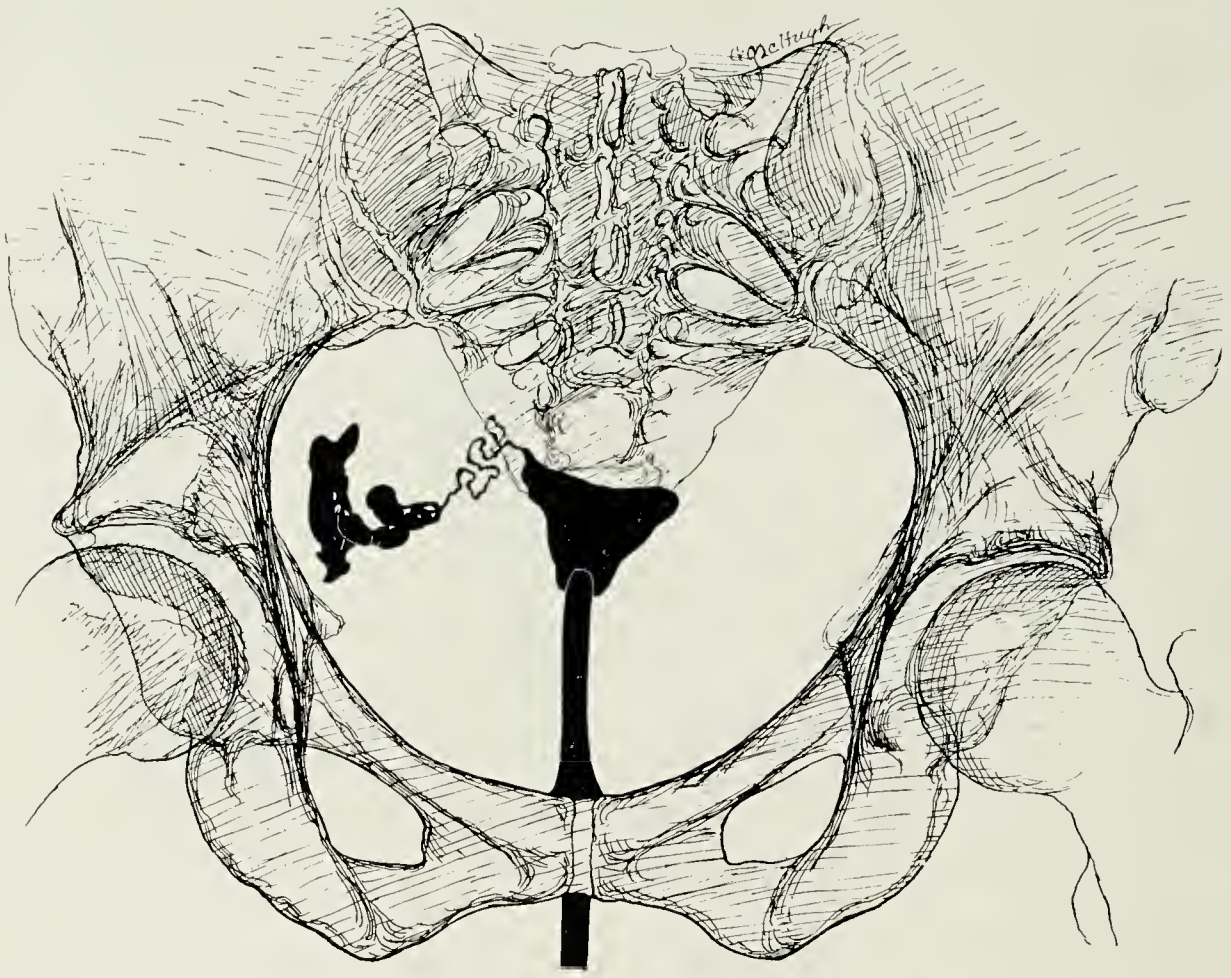
A



B

Fig. 17.—*A*, Normal hysterosalpingograph. The uterine cavity and both fallopian tubes are completely filled and normal in appearance. Sphincter-like structures at cornual ends of tubes are visualized clearly. *B*, Roentgenogram of the same patient 24 hours after the injection of opaque oil. Note the characteristic spread of the contrast medium among pelvic cavity viscera indicative of tubal patency.

Marked irregularities of the lumens are common with stricture formation. Calcified concretions are often seen. If both tubes fail to visualize



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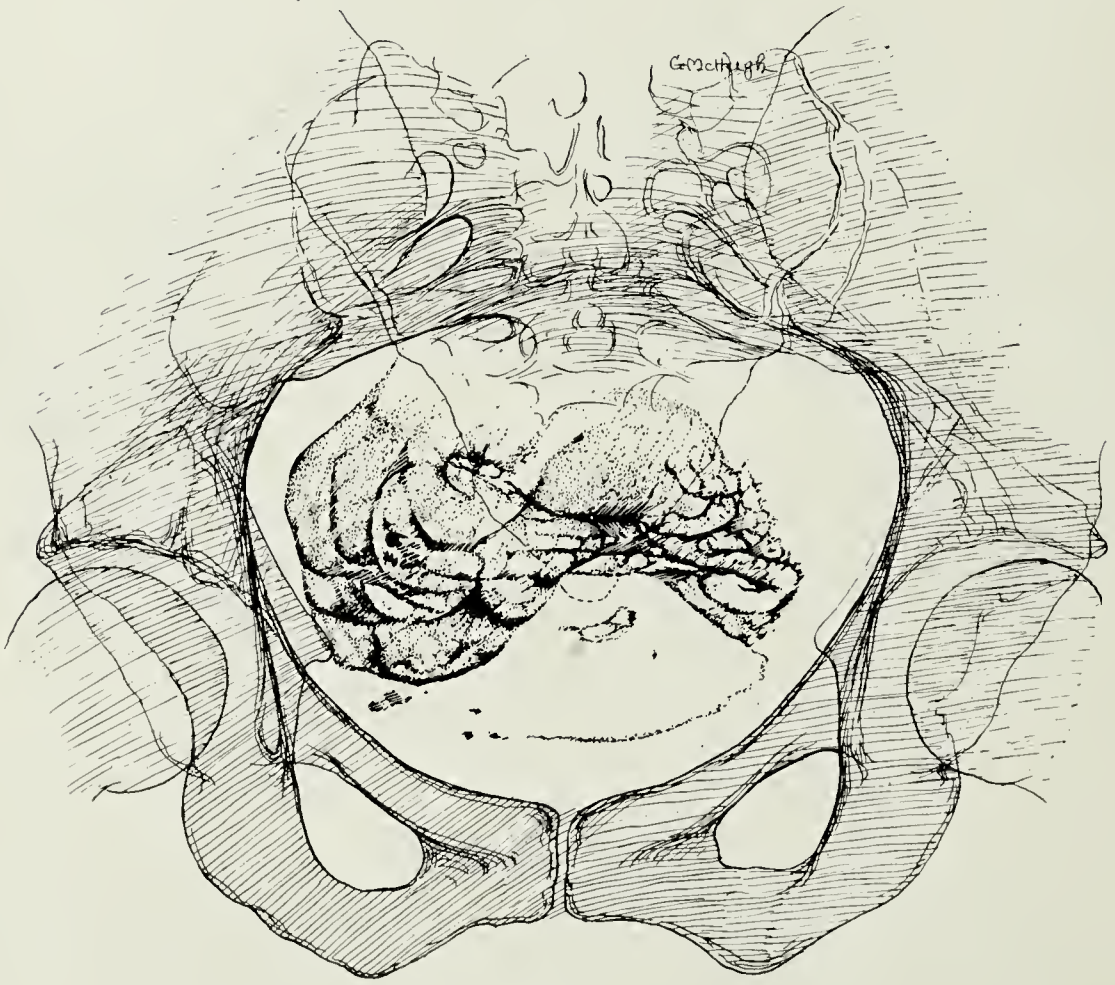


B

Fig. 18.—*A*, Normal visualization of the uterine cavity and the left fallopian tube. The other tube is not visualized because of blockade in the cornual region. *B*, Characteristic spread of the contrast medium among pelvic viscera indicative of tubal patency.

with the uterus in marked retroversion, the examination should be repeated at a later time before tubal blockade is diagnosed (Figs. 17 to 20).

The Study of Ovarian Function.—When the state of the reproductive organs has been evaluated, the next step is to determine if they function normally. It is important to study ovarian activity first, because a mature ovum must be produced periodically for normal fertility. Individuals who menstruate regularly usually ovulate regularly. There may be periods during which ovulation is suppresed, but this does not occur often in the woman who has a normal menstrual pattern. However, if the periods are irregular, of very short duration or the flow scant in amount, ovulation may or may not occur at regular intervals.

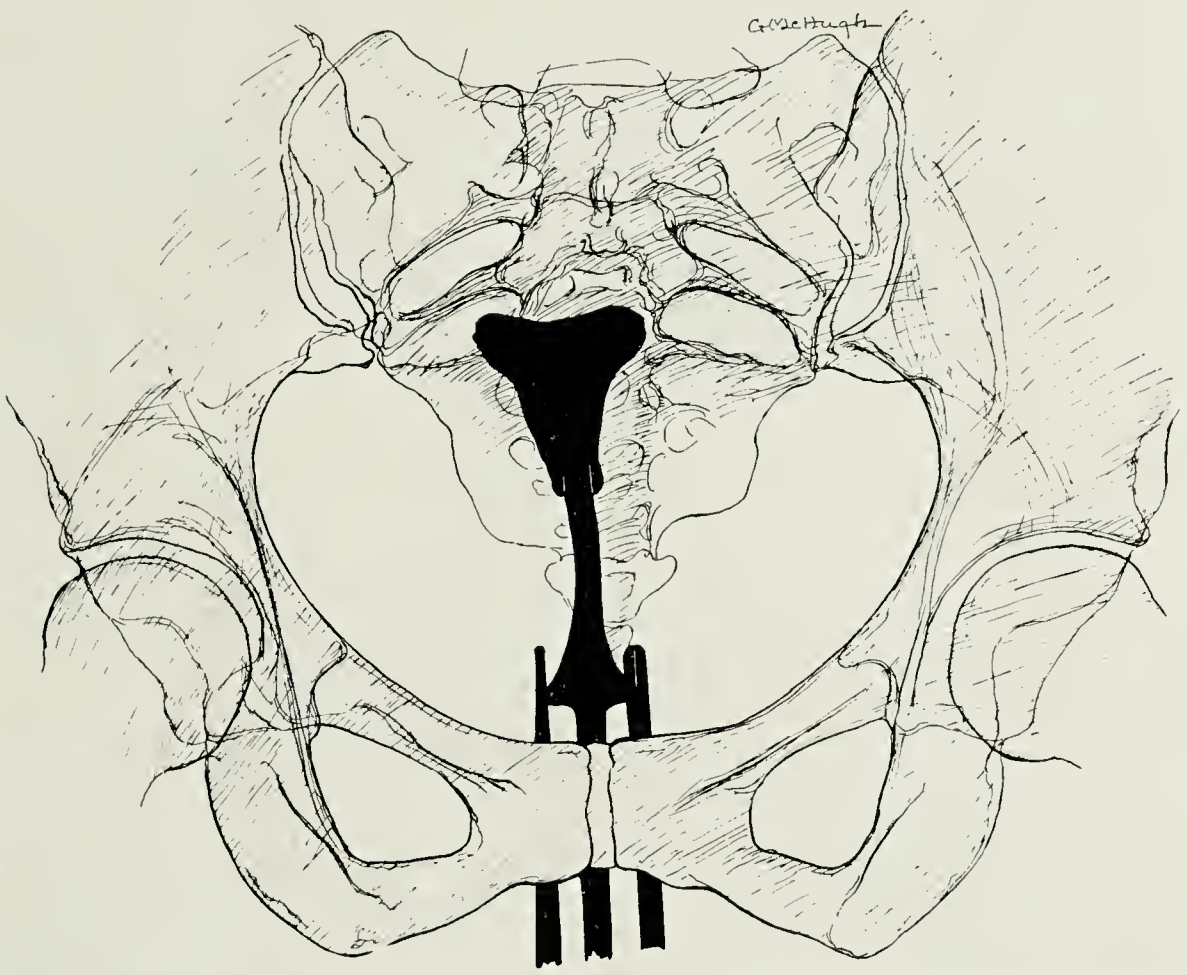
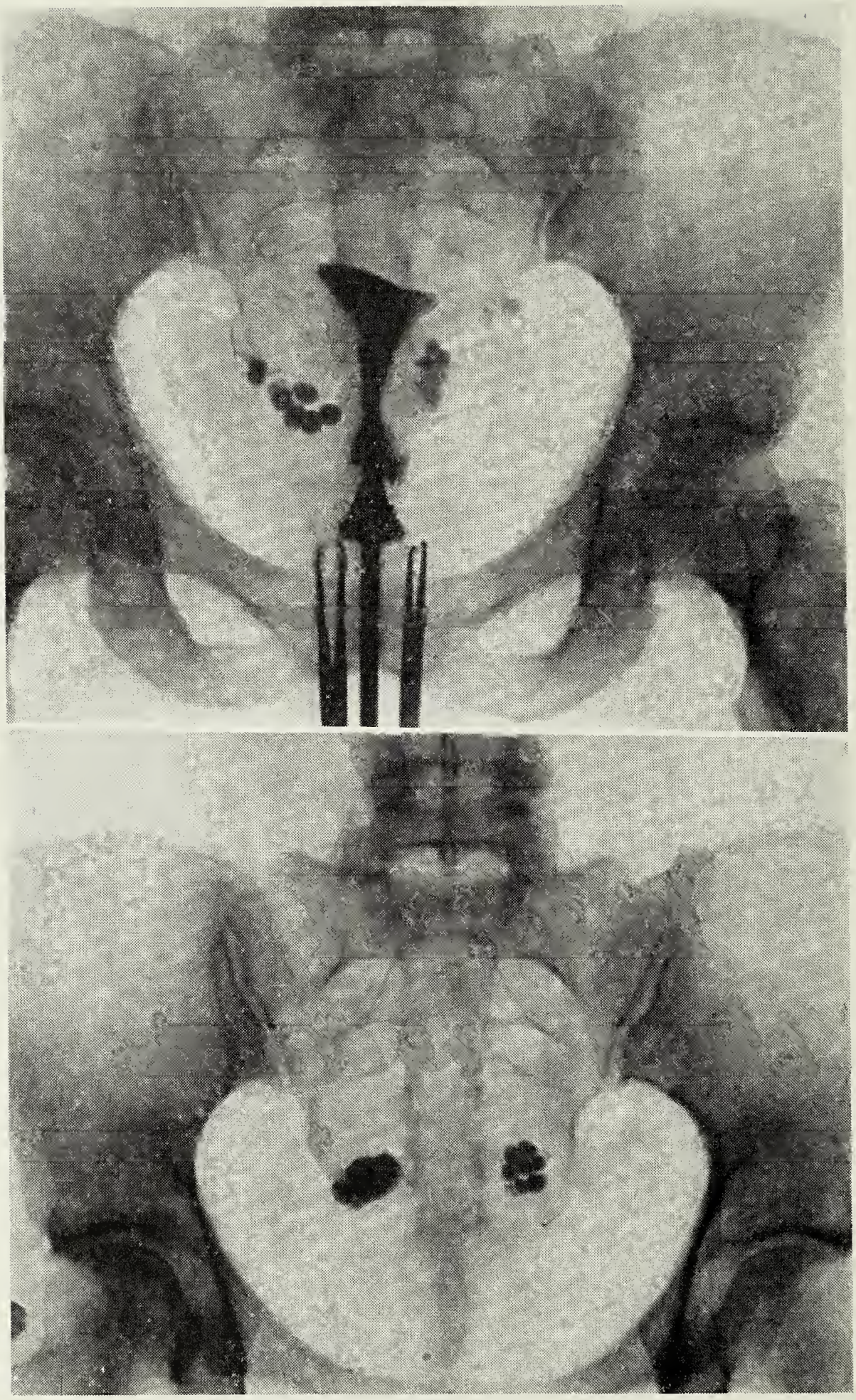


Fig. 19.—Hysterosalpingograph showing normal filling of the uterine cavity but neither fallopian tube is visualized.

The occurrence of ovulation can be demonstrated in several ways.

Endometrial Biopsy.—In the first place one may obtain a small biopsy of the endometrium at the onset of bleeding and a histologic study of this biopsy will reveal what has occurred in the ovary during the current cycle. The endometrium mirrors ovarian activity, for under the influence of the developing follicle and the estrogen it produces the uterine mucosa grows rapidly. However, with the rupture of the mature follicle and the release of the ovum, the lutein cells of the developing corpus luteum produce progesterone and under its influence the endometrium changes into the progestational phase with tortuous secretory glands and decidua-like stroma cells. At the onset

A



B

Fig. 20.—*A*, The uterine cavity and fallopian tubes are visualized but there is a marked dilatation of the distal ends of the tubes with hydrosalpinx formation. Note the droplet formation produced by oil mixed with fluid and indicative of a hydrosalpinx formation or walled-off fluid. *B*, Roentgenogram taken 24 hours later showing the droplet formation and the absence of a characteristic smear.

of menstruation this secretory phase of the endometrium has reached its greatest development. Obviously, if the biopsy at this time shows no evidence of progestational development, ovulation did not occur in the current cycle and the bleeding is anovulatory in character. Biopsies of the endometrium can be taken in the office by a small punch forceps or a suction curet, and the procedure may be repeated many times.

Progesterone Metabolism.—The occurrence of ovulation in the cycle can be established by a study of the progesterone metabolism. This hormone produced by the ovarian follicle after its rupture is converted to pregnandiol and is eliminated in the urine as pregnandiol glucuronidate. Chemical methods are available for its quantitative determination. Prior to ovulation little of this substance is present in the urine. Following ovulation as much as 5 to 10 mg. can be obtained daily. The quantitative estimation of the amount of pregnandiol glucuronidate in the urine for forty-eight or seventy-two hours will establish the presence of an active corpus luteum and ovulation.

Both of these methods are laborious and provide indirect evidence at best. Furthermore, they provide information about ovulation some time after it has occurred. Most recently a physiologic phenomenon has been adapted to denote ovulation. Its simplicity has provided us with a most useful tool in the study of sterility.

Body Temperature Records.—Body temperature variations occur in healthy individuals young and old. The temperature is a sensitive barometer of physical, mental and physiologic activity. Muscular activity, mental excitement, food taking and extraneous stimuli will tend to raise the level of the body temperature. Rest and sleep will tend to lower it. Normally, the temperature curve over a twenty-four hour period will tend to be elevated during the day and lowered at night. This diurnal pattern is due to the fact that the days are devoted to activity and the nights to rest.

In the healthy male the characteristic curve will be present day after day. In the female, however, ovarian activity influences the basal body temperature. Follicle rupture and corpus luteum formation tend to raise the temperature so that the curve is at a higher level the latter half of the cycle than during the first half. This physiologic phenomenon has been adapted to the study of fertility, endocrine problems and as a means of birth control.

The patient is asked to indicate on a specially prepared graph the menstrual days, any unusual occurrence, illness, coitus and special medication. She should buy a good thermometer, the scale of which is easy to read. Immediately on awakening in the morning, before stirring from bed and before smoking, drinking or eating she should place the thermometer in her mouth for five minutes and promptly read and record the temperature by placing a dot opposite the proper date. Any unusual occurrence should be noted opposite this recorded dot. These

daily oral temperature readings will provide the curve from which ovarian function can be interpreted.

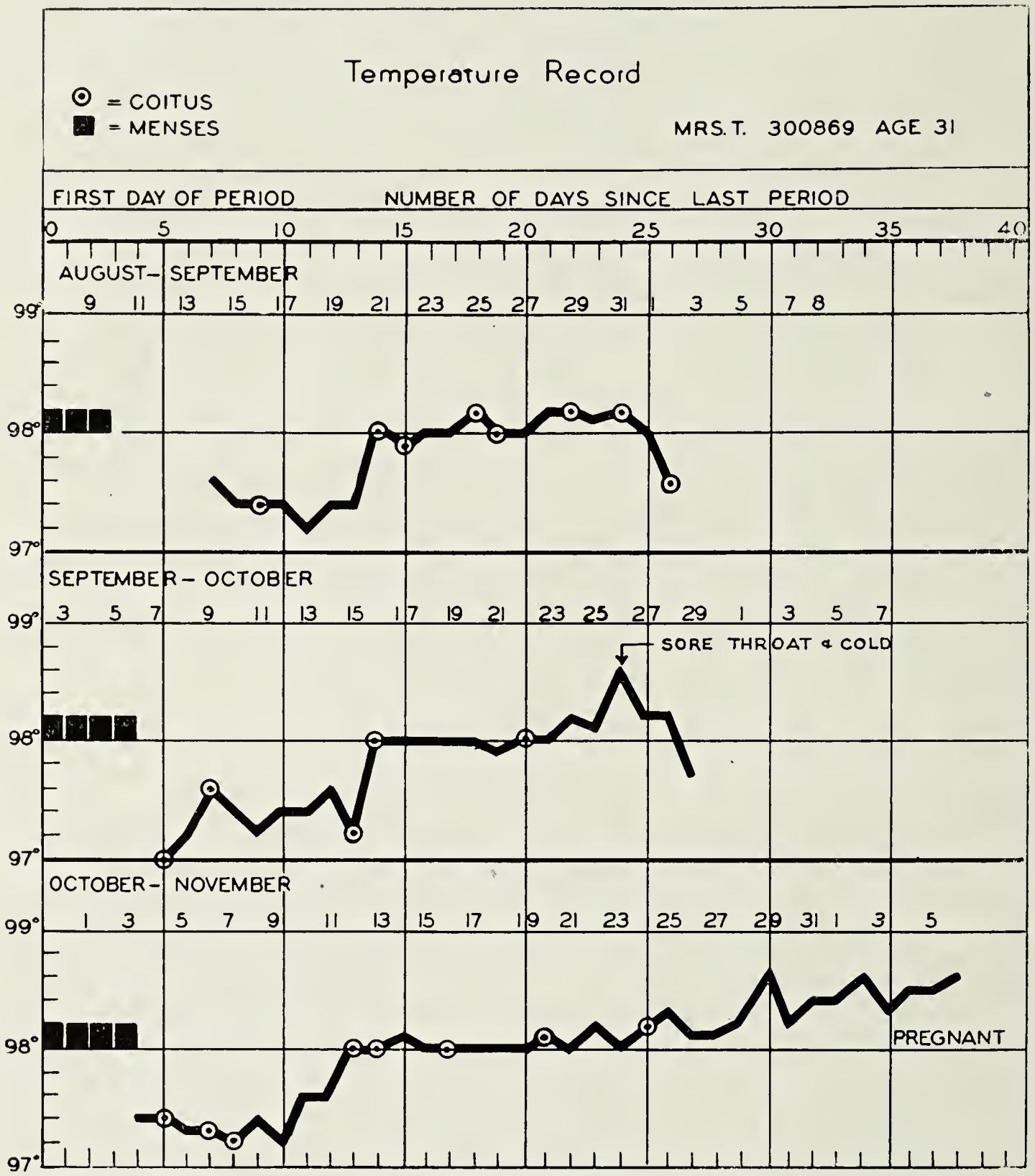

Temperature Record
= COITUS
= MENSES
MRS. T. 300869 AGE 31
FIRST DAY OF PERIOD
NUMBER OF DAYS SINCE LAST PERIOD
0 5 10 15 20 25 30 35 40
AUGUST– SEPTEMBER
9 11 13 15 17 19 21 23 25 27 29 31 1 3 5 7 8
99°
98°
97°
SEPTEMBER – OCTOBER
3 5 7 9 11 13 15 17 19 21 23 25 27 29 1 3 5 7
SORE THROAT & COLD
OCTOBER – NOVEMBER
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 1 3 5
PREGNANT

Fig. 21.—Basal temperature record of a patient who could not become pregnant. The graph covers three monthly cycles. The dark blocks indicate the menstrual days. Note that in August the temperature remained under 97.6° F. until the twelfth day after the beginning of menstruation when it suddenly began to rise, reaching the plateau on the thirteenth day. It remained elevated until day twenty-five when it began to drop, followed by menstruation 36 hours later. The rise in temperature is indicative of the rupture of a mature follicle in the ovary, the discharge of the ripe egg, and the formation of a corpus luteum.

In October, no drop in temperature occurred. The continued elevation indicated that the egg had become fertilized and that the patient was pregnant.

The basal temperature is at a low level during menstruation and during the preovulatory period. It may be as low as 97° F. but usually

it varies between 97.4° and 97.8° F. During the twenty-four hour period when ovulation occurs the temperature rises abruptly, reaching a level 0.6° or 1.0° above the low point, following which it will remain elevated. About twenty-four to thirty-six hours prior to the onset of active menstruation an abrupt drop will occur. Some investigators have noted a small drop of the temperature just prior to the ovulatory rise and have interpreted this point as the ovulatory period. This may be so, but the rise in the temperature and its maintenance at the post-ovulatory level is due to progesterone. The period of the temperature change is the fertile period when conception can take place. Should pregnancy ensue no premenstrual drop occurs, the temperature remaining elevated (Fig. 21).

An accurate temperature record over a period of several months will provide evidence concerning ovulation in most women. Furthermore, it provides the patient with knowledge about her fertile period. The physician will obtain pertinent information concerning the menstrual pattern, the sex life of the couple, medication and her daily routine, and he will be able to offer intelligent advice.

Thyroid Function.—The thyroid gland is intimately associated with the glands of internal secretion which control the reproductive organs. The gonadotrophic function of the pituitary gland is dependent on normal thyroid activity. A basal metabolic determination should be part of every sterility study.

THERAPY

The treatment of infertility depends primarily on a careful evaluation of the anatomic and physiologic factors which enter into the function of reproduction. Complete sterility investigation of the husband and wife is the major part of therapy. In more than one-third of the couples investigated a few simple suggestions suffice to obtain the desired results. In a smaller group continued observation and treatment are necessary. At least one-third of the couples examined have unsurmountable obstacles to conception which only the relentless march of scientific progress will ultimately remove.

The Patient with Normal Reproductive Organs.—About one of every three women examined has reproductive organs that are within normal limits, anatomically and functionally. Her husband is found to be of average fertility. This couple is instructed to study the fertile periods as indicated by the temperature graph and to time coitus to the periods of optimal fertility, during the period of temperature shift. If coitus has taken place at too frequent intervals, or if the study of the husband indicates that he is of low fertility, it is desirable to restrict intercourse to the period of fertility indicated on the temperature graph. The short life of the ovum and the spermatozoon makes it necessary to restrict fertile matings to a very short period of the average cycle. Such simple advice has yielded many happy results.

If the patient has a low basal rate, thyroid extract may be prescribed. We have used the following empiric therapy: one grain of thyroid extract daily for every —10 of the basal rate, i.e., —10 or less, one grain daily; —10 to —20, two grains daily, etc. The couple should be urged to spend much time in the open, exercise intelligently, eat an adequate balanced diet and refrain from worry. A high percentage of the women of this group will return within six months having missed a period, their temperature curves remaining at a high level (Fig. 21), and pregnant.

The Patient with Partial Barriers to Conception.—The second group of couples seeking relief of sterility have many factors which decrease the level of fertility but they are not necessarily permanently sterile. Some of these women are married to *husbands of low fertility.* Sperm counts in the range of fifty million associated with a high incidence of abnormal forms are an index of low fertility. Everything should be done to improve fertility in the male.

Many clinical findings may not be absolute barriers to conception but they may impede it and decrease the level of fertility. All of the factors which can be corrected should be treated. The physician must evaluate carefully the risk involved in the correction of some condition present and the importance that its presence plays in the inability of the patient to conceive. Thus, *infections of the lower genital* tract should be eradicated. An endocervicitis or an erosion of the cervix should be cleaned up by means of the cautery. Deep-seated infections of the glands of the endocervix with the formation of a pin-point os and the accumulation of a thick, glary, infected mucus plug may have to be treated by conization. Nevertheless, few patients who have had extensive conization procedures conceive. Possibly, the removal of a large portion of the endocervical mucosa interferes with normal mucus secretion and the transport of spermatozoa into the fallopian tubes.

Malpositions of the uterus not associated with inflammation and fixation of the structures rarely decrease fertility. No serious harm can come from the manual replacement of the uterus in an anterior position and its maintenance in this more common position by a suitable Smith-Hodge pessary. Postural exercises may accomplish the same thing, with or without the aid of a pessary. Surgical correction of retrodisplacements should be recommended rarely for the simple purpose of altering the relationship of the uterus in the pelvis. When other surgery is indicated anterior uterine suspension may be carried out at the same time.

Neoplasms of the uterus are found frequently in women who cannot conceive. However, it can be said rarely that the tumors are the cause of the lack of fertility. Women with sizable tumors get pregnant without difficulty. However, at times the surgical removal of several tumors in a woman who has not been able to conceive for many years is promptly followed by a pregnancy. In the last year Victor Bonney in

England and Rubin in this country have stressed the value of removing fibroid tumors in childless women. One should be certain the fallopian tubes are normal and patent, that the patient is fairly young (less than 35) and that she has normal ovarian function. Furthermore, one cannot always promise to remove the tumors and leave a uterus sufficiently intact to allow childbearing.

The *endocrine deficiencies* are much more difficult to correct than are the organic defects. Ovarian failure in mild degrees can be improved by a regimen of proper living, diet, weight reduction in those overweight and thyroid extract where indicated. Serious degrees of ovarian failure with scant or irregular menses, an absence of menstruation and a lack of ovulation are treated very unsatisfactorily. True, every hormonal preparation has been recommended. Some good results have been reported but none has stood the test of experience and scientific investigation. The treatment of ovarian failure will have to wait upon the development of a gonadotrophic principle from the hypophysis sufficiently potent to produce follicle growth, maturation and ovulation in the human ovary. No such preparation is available commercially today.

The Patient with Absolute Barriers to Conception.—The third group of couples studied for sterility have insuperable factors which make childbearing impossible. The most common finding in women is *tubal blockade* as a result of preexisting pelvic infection. Where both fallopian tubes are closed, pregnancy is not possible. The tubal closure can be present at the cornua and neither tube will be visualized or at the ostium with minor or gross malformations of the tube. If after repeated examination the tubes are definitely closed, the patient should be told that pregnancy is most unlikely. She should be urged to consider adoption or, in suitable cases, salpingostomy. The reconstruction of closed fallopian tubes has been more successful of late. Newer surgical approaches will provide better results. One must remember that restoring tubal patency is not synonymous with increased fertility, for the mucosal lining of the tube may have been so altered by infection and healing that it is no longer suitable for the transport of the ovum and spermatozoa.

The second most common cause for permanent sterility is an *absence of spermatozoa in the seminal fluid*, or so few that the husband can be considered sterile. Urologists have little to offer these individuals. In a few where a blockade is present, delicate operations have been devised which may offer some success. Much work remains to be done on male infertility. Patients who are married to husbands who are sterile should be told that pregnancy is unlikely and that three courses are open to them. In the first place, they may so arrange their lives that other interests take the place of children. Many couples can make the necessary adjustments if the physician is frank with them. Their second choice is to consider the adoption of one or two babies. Lastly,

they can consider artificial insemination with donor sperm. More and more childless couples in which the husband is at fault look with favor on this last possibility, for artificial insemination offers them an offspring who has the genetic qualities of the wife plus whatever values may accrue from the environmental factors of its first nine months of intrauterine life. Where the husband and wife choose this approach to a family the physician should carry out the necessary procedures, or better still, he should refer the couple to some individual who has the facilities for such specialized work.

Other causes for permanent sterility may be found. *Ovarian failure* with complete absence of menstruation and ovulation is usually a permanent barrier to childbearing. Major malformations such as the absence of the vagina or uterus are occasionally found. Women consult physicians for the relief of sterility after operative procedures which entailed the removal of the fallopian tubes. Little can be offered these patients for there are no good methods by which the ovum can be directed into the uterine cavity in the absence of a fallopian tube. These women, after a complete study, should be told about their state as regards childbearing so that they may reorient their lives and not waste time and money on fruitless medical efforts.

IRREGULARITIES OF UTERINE BLEEDING AND THEIR TREATMENT

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What Nature has established as average menstrual chronology is regarded too commonly as a norm for health and for fertility. Inflexible rhythmicity or uniform fertility does not characterize the cycles of any normal woman. A woman may menstruate only two or three times a year and yet she may be healthy and able to conceive. Irregular bleeding, on the other hand, may be a symptom of organic, endocrine or local disease or it may result from functional disturbances of the ovaries or the endometrium. It is therefore necessary to differentiate vagaries of normal function from clinically significant abnormalities of uterine bleeding. Unless this is done, treatment is solely symptomatic, is often unnecessary, and is always founded upon the objectives of securing menstrual calendars which conform to the average concept of normality.

GENERAL CONSIDERATION

The term "menstrual irregularities" was avoided in the title of this discussion for the purpose of emphasizing that, whereas some irregularities concern only chronology and do not involve the quality of ovarian function and are truly menstrual irregularities, irregularities in general may embrace disturbed chronology, qualitative alterations of function, and alterations in bleeding.

Irregularities vary according to their effects upon the ovarian cycle: (1) The nonbleeding, or interval, phase may be altered. (2) The phase of bleeding may be changed. (3) The cycle may be absent—amenorrhea.

Irregularities of the interval phase are of two types: (1) There is disturbed chronology which involves the preovulatory or estrogen phase without disturbing the progestational phase, the result being eventual ovulation and progestational or menstrual bleeding. (2) The quality of ovarian function is altered with the result that there may be ovulation followed by deficient progestational activity, or ovulation may not occur and the subsequent bleeding is estrogenic in type, or there may be reduced estrogen secretion, that is, hypoestrogenism, terminated by bleeding from poorly proliferated or hypoestrogenic endometriums.

Irregularities of the bleeding phase may be of three types: (1) The duration may be altered. (2) The amount of blood loss may be

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changed. (3) Bleeding may occur from progestational or from proliferative or estrogenic endometriums.

Amenorrhea may be of three types: (1) It may be physiologic, resulting from immaturity (preadolescence) or from senility (postmenopausal). (2) It may be initial and be characterized by hypopubescence or apubescence. (3) It may be intercurrent, developing during the reproductive epoch.

These irregularities may assume clinical significance for the following reasons: (1) They may result in depleting uterine hemorrhages. (2) They may be associated with undesired impairment of fertility. (3) They may be associated with psychosomatic disturbances. (4) They may be symptoms of organic or endocrine disease or of local involvement.

THE GYNECOLOGIC INVESTIGATION

Abnormal bleeding is a symptom to be investigated and evaluated rather than a disease which requires empiric treatment. Most women, whose cycles are fairly rhythmic and whose flowing is not excessive, have qualitatively normal ovarian function. Many women, whose cycles are irregular and whose flowing is excessive, have qualitatively abnormal ovarian function. These generalizations, however, are not applicable to the individual.

A "functional disturbance" should not be predicated or diagnosed save when inclusive objective studies have not identified organic disease or local pathologic change. Age and marital status of a patient often suggests etiologic probabilities. Irregular bleeding during adolescence usually is functional, often physiologic, and less commonly endocrinal. During the early years of marriage, gestational complications and gynecologic infections are common causes. During the latter part of the reproductive epoch, neoplasia should be suspected and ruled out, although functional disturbances are common. During the climacteric, there are physiologic functional disturbances, which should be segregated from those due to intercurrent disease, particularly neoplasia. Indeed, the quality of the ovarian function of essentially cyclic women should be investigated when they are unable to conceive, and especially when other sterility studies have been negative.

Investigations of disturbances of bleeding go beyond the confines of a gynecologic speculum; indeed, the pelvis may not be always a correct diagnostic oracle. A meticulous history provides valuable data and a detailed medical examination is essential. Disturbed bleeding may be one of the earlier symptoms of medical disease or of metabolic disturbance. Anemia and other blood dyscrasias, pulmonary tuberculosis, deficiency diseases, and obesity are some of the medical conditions which are associated with disturbed flowing. A neuropsychiatric inventory should not be overlooked, since major psychopathies, as well as cachexia nervosa, anxiety neuroses and emotional crises may upset the ovarian function.

History.—The gynecologic inquiry should be inclusive with full data in regards to specific dates of bleeding and past and present treatments—surgical, gynecologic or endocrinal. Often previous estrogen therapy with subsequent episodes of estrogen withdrawal bleeding obfuscate the history and render impossible the differentiation of spontaneous and artificial flowings. When there is definite acyclicity, these data are important: duration of the longer cycles, of the shorter cycles and of average cycles; dates and durations of the longest and shortest cycles; duration of the longer episodes of bleeding, of the shorter episodes of bleeding and of the average; duration and dates of the longest and shortest episodes of bleeding; and estimates of the amount of bleeding (as saturated pads or as times normal) during longer, shorter and average episodes of bleeding. When specific data cannot be secured from a patient, and if there is no gravity of the irregularity, it is helpful to have a patient keep these specific records and return later for an evaluation of her problem. When the question of excessiveness of flowing arises, prebleeding and postbleeding estimates of hemoglobin and of red cell counts may provide information on hematopoietic drain.

A thoughtful gynecologist may ask wisely this question of the patient: "Why does your irregularity disturb you?" The answer of the patient may be all-important and it may lead to a proper evaluation and posing of her problem. It often clarifies psychosomatics. The history and pelvic examination should afford ready differentiation of bleeding due to pregnancy and its complications and that of strictly gynecologic nature.

What the patient considers genital bleeding may not be of this nature. Urogenitorectal topography is localized vaguely by many women. Pelvic and rectal examinations and inspection of the urethral meatus should differentiate between vaginal, rectal and urethral bleeding.

Pelvic Examination.—A pelvic examination is an obligatory part of the investigation of disturbed flowing. Inspection should reveal bleeding of traumatism. Bleeding due to vaginitis is identified by speculum examination. Cervical lesions, as polyps, erosions, ulcerations and carcinomas, are apparent on speculum examination. Polyps should be studied by a pathologist lest they may be malignant. Areas of cervical ulceration and leukoplakia should be biopsied and should be subjected to pathologic studies. Bimanual examination recognizes irregularities and enlargements of the uterus which may result from neoplasia. Adnexitis, quite commonly associated with disturbances in bleeding, is diagnosed during the bimanual examination. A careful palpation in the ovarian region discloses tumors and cysts of the ovaries which may be related etiologically.

Vaginal Smears.—Cytologic studies of the vaginal fluid, secured by repeated vaginal smears, are valuable in the investigation of obscure malignancies of the genital system of women in the late reproductive

epoch and during the climacteric. Vaginal smears, in our opinion, offer little practical, clinical information regarding ovarian function: far more worthwhile data are secured from studies of daily temperature graphs and from studies of endometrial biopsies.

Uterine Curettage.—Curettage of the uterus is not a necessary part of the investigation of all irregularities. Women, thirty-five years of age or older, who have too frequent, prolonged, or excessive bleeding should be curetted thoroughly and all of the endometrium should be studied by a pathologist, lest a malignancy of the endometrium be overlooked. Repeated curettages may be necessary to be convinced that no malignancy exists in pre- and postmenopausal women. The cervical canal also should be curetted. When it is possible, curettage should be done at the onset of an episode of bleeding, within the first twelve hours, in order that function may be estimated as well as cytological studies done. When irregular shedding of the endometrium is considered a likely cause of prolonged bleeding, a curettage on the third to fourth day after the onset of flowing should reveal persistence of progestational elements. Curettage in patients with long-standing intercurrent amenorrhea may be advisable in view of the fact that occasionally tuberculous endometritis may be found. In general, curettage is done too frequently in the investigation of this particular disturbance of flowing.

Endocrine Inventory.—Since the gynecic functions of the reproductive epoch are monitored by the ovaries in particular and by the endocrine system in general, endocrine inventory is necessary for an assessment of disturbed flowing. The history and physical examination will disclose errors of development and hypoplasia of the genital organs. Actual measurements combined with estimation of the uterocervical ratio provide dimensional objectiveness to genital hypoplasia. Clinical findings and the results of the basal metabolism test and of serum cholesterol studies should establish thyroid disease. Roentgenograms of the sella turcica should be done routinely because, despite normal findings in most patients, they prove valuable by the occasional disclosure of unsuspected pituitary tumors. When there is apubescence or hypopubescence, the osseous age should be estimated from appropriate roentgenograms. End organ insufficiency should be differentiated from endocrine deficiency: hypomastia or uterine hypoplasia may occur in women with normal glandular functions.

Basal Temperature Studies.—Studies of daily basal temperature values during several ovarian cycles afford an excellent and practical means of screening the quality of ovarian function. These studies permit differentiation of menstrual irregularities (ovarian cycles characterized by ovulation and bleeding from progestational endometriums) and of irregularities associated with nonoccurrence of ovulation and with estrogenic bleeding. Basal temperature data also may be used to follow responses to specific therapy. Failure of the basal temperature

to drop significantly prior to the onset of bleeding may suggest that bleeding is associated with "irregular shedding of the endometrium." In this condition, it is said that the secretion of progestin (and the urinary excretion of pregnandiol) continues after the onset of bleeding for several days. Biphasicity of the temperature graph of the normal cycle is well known. The hyperthermic phase is due to the secretion of progestin following ovulation. An artificial hyperthermic phase may be induced by progestin therapy.

Endometrial Biopsy.—Endometrial biopsy is valuable in the investigation of disturbed flowing. We do not feel that biopsy is obligatory in the investigation of disordered bleeding during adolescence, since these disturbances may be accepted as functional. The biopsy technic should not supplant curettage in the investigation of prolonged, too frequent or excessive bleeding in the woman 35 years of age or older. Here the most important problem is the diagnosis of organic disease, in particular malignancy. The endometrial biopsy is unsuited for this and it should not be used to diagnose pathologic states. Its sole indication is the estimation of function. Endometrial biopsy should be done within the first twelve hours of flowing when irregular bleeding is being investigated. The more irregular a patient is, the more important biopsy becomes at the onset of bleeding. When cyclic women are being investigated—and this is usually in the course of sterility studies —spot biopsies three or four days before the onset of bleeding may be employed. It is necessary to confirm the subsequent occurrence of bleeding at the expected time in order to interpret properly findings based on spot biopsies. Repeated or serial biopsies during amenorrhea may be advisable for the purposes of identifying any spontaneous cycle which might be occurring. A single biopsy during amenorrhea may give two valuable types of information: (1) the degree of estrogen stimulation (whether the endometrium is hypoestrogenic, euestrogenic or hyperestrogenic); (2) whether there is local disease as tuberculous endometritis. The data from endometrial biopsy correlate well with those of basal temperature studies and are mutually complementary. Indeed, if a woman supplies basal temperature data which are unequivocally normal, a biopsy test is hardly necessary.

If basal temperature data or endometrial biopsy indicate that prolonged or excessive bleeding is associated with a progestational endometrium, then there is little probability of endocrine disease or disturbance of endocrine function, and the likelihood of organic disease of the endometrium as polyp, submucous fibromyoma or irregular shedding, should be ruled out by a careful curettage.

When basal temperature data indicate a shortening of the progestational phase, endometrial biopsy, taken at the onset of bleeding, should disclose an immature or poorly differentiated progestational endometrium.

Studies of Hormonal Levels.—Studies of hormonal levels are of little or no value save in the investigation of apubescence, hypopubescence, or intercurrent amenorrhea. Studies of urinary gonadotropins yield very valuable information in these conditions. Normal gonadotropin levels (eugonadotropuria) indicate constitutional and extra-endocrine etiology. Low gonadotropin levels (hypogonadotropuria) indicate pituitary deficiency. Elevated gonadotropin levels (hypergonadotropuria) indicate intrinsic ovarian failure with compensatory hyperactivity of the pituitary. When the urinary gonadotropins are two- to three-fold increased, the ovarian failure may be temporary and may be overcome eventually with treatment or by the increased pituitary function. When the elevation of urinary gonadotropins is more marked—from five- to fifty-fold—quite uniformly the ovarian failure is irreversible and treatment will prove of no avail. This is true for apubescence and hypopubescence; and when these elevated values are encountered in women who have ceased to menstruate, the diagnosis and prognosis of premature menopause is warranted.

Studies of urinary pregnandiol levels when irregular shedding of the endometrium is suspected may give information complementary to more readily secured data of basal temperature levels and of biopsies and curettages, done three to four days after the onset of flowing.

IRREGULARITIES OF THE INTERVAL

The interval of the normal menstrual or ovulatory cycle is characterized by two phases of growth and a terminal phase of regression, namely: (1) a preovulatory estrogen phase, (2) a postovulatory estrogen and progestin phase, and (3) a terminal regressional phase, due to withdrawal of estrogen and progestin. Estrogen is the true growth hormone of the endometrium. When an endometrium is under active stimulation by estrogen, it grows and regression and bleeding do not occur. Progestin, which is secreted by the corpus luteum following ovulation, brings about differentiation of the endometrium preparatory to possible nidation. When there is a waning of estrogen and progestin levels, incidental to regression of the corpus luteum, the endometrium begins to regress and eventually bleeding occurs. The duration of the postovulatory of progestational phase is quite uniform; it does not vary much from fourteen days. The estrogen phase of the cycle, however, is much more variable. Indeed, all of the significant variations in cycle length are due to variabilities in the estrogen or preovulatory phase.

Irregular Chronology of the Cycle.—Ovarian cycles may occur too frequently or quite infrequently and yet the quality of ovarian function may not be disturbed: ovulation occurs and the progestational phase lasts approximately fourteen days with the result that cycles remain fertile. These cycles are truly menstrual. The variability of these cycles apparently results from the ease or the difficulty with which the "favored follicle" is matured. The intensity of the hormonal

stimulus (pituitary gonadotropin) or the receptivity of the end organ (the follicle), or both, determine the length of the estrogen phase. Once ovulation occurs, however, the duration of the rest of the cycle is predetermined.

Disturbed chronology per se is of no clinical significance. If infrequent menstrual cycles are proved not to be the result of constitutional disease, their only impact may be upon the fertility or the psychosomatics. A patient who has two ovarian cycles a year instead of twelve is two-twelfths as apt to become pregnant. Periodicity of uterine bleeding is not an essential to good health, despite the belief to the contrary of many women. Prolonged phases of hypothermia, however, may have psychosomatic components. Evidence exists also that the psychosexual pattern under these circumstances is altered. Despite these facts, infrequent or too frequent cycles, when associated with normal ovarian function, should be left alone from the standpoint of therapy. These cycles may represent the best adjustment which a patient's ovaries can make to the stimuli of her pituitary gland. Treatment may disturb this adjustment and may result in irregular anovulatory or sterile cycles.

Bleeding may occur during the interval of menstrual cycles without disturbing the quality of ovarian function. Interval bleeding may occur from local pathologic conditions, as a polyp or a submucous fibromyoma. Interval bleeding, varying from slight spotting to several days of fairly free bleeding, may occur at the time of ovulation. Interval bleeding, therefore, may obfuscate a hormonally normal cycle and lead erroneously to the assumption of disturbed ovarian function. Studies of basal temperature curves, however, should demonstrate the normalness of ovarian function.

Abnormal Quality of Ovarian Function.—There may be disturbed ovarian function in cycles of normal chronology as well as in cycles of disturbed chronology. Three types of disturbed ovarian function are recognized: (1) deficient progestational phase, (2) anovulation with normal estrogen function, and (3) anovulation with deficient estrogen function.

A deficient progestational phase results from inadequate function of the corpus luteum. This usually is due to the formation of a faulty corpus luteum or to premature regression of the corpus luteum. There results a short corpus luteum phase, which is reflected in the basal temperature curves by a short hyperthermic phase. Endometrial biopsy studies indicate terminal bleeding from endometriums which have not reached full progestational differentiation. Ovarian cycles with short progestational phases may result in apparent sterility, due in reality to early abortion because of incomplete preparation of the endometrium for nidation. In many instances, the fertilized egg may reach the endometrium after it has already begun to regress prior to the onset of bleeding. Under these circumstances, a short progestational phase may be amplified by substitutional therapy with progestin and estrogen.

Anovulation with normal estrogen function occurs when a follicle develops to the point of ovulation and then fails to rupture. This may be the result of an error in the hormonal stimulus or a fault of the end organ, the ovary. In the anovulatory cycle, there is no corpus luteum function and, therefore, no progestational differentiation of the endometrium. Terminal bleeding occurs from an interval or estrogenic endometrium. The cycle may be of normal duration, short, or unusually long duration. Its primary significance is in the absolute sterility which is imposed on the patient. Treatment is indicated when this sterility is undesired. The aim of therapy is to stimulate ovulation and corpus luteum function.

Anovulation with deficient estrogen function results when development of a follicle ceases prior to its reaching maturity. Its hormonology and clinical significance are the same as those just discussed. Terminal bleeding occurs from endometriums lacking full estrogen stimulation, that is, hypoestrogenic endometriums. (Anovulatory cycles may be physiologic for several years after the menarche and during the premenopausal phase of the climacteric.)

IRREGULARITIES OF FLOWING

Regression and bleeding terminate the menstrual cycle, because a critical waning of estrogen levels renders further endometrial growth impossible. As a rule, a fall of 50 per cent in estrogen levels from peak values is followed by bleeding. Accordingly, estrogen values do not approach zero at any time during menstruation. Menstrual bleeding ceases when estrogen levels rise, incidental to the maturation of "clusters" of follicles, prior to a selection of a "favored follicle." Failure of this normal hemostatic mechanism results in prolonged flowing.

Anovulatory cycles are monitored solely by the waxing and waning of levels of follicular estrogen. While the follicle is actively growing, ample estrogen for endometrial growth is supplied. When the follicle regresses, without ovulation, endometrial regression begins and is followed eventually by bleeding.

Irregularities of bleeding may concern (1) its duration, (2) its amount, (3) the type of endometrium from which it occurs.

Abnormal Duration of Bleeding.—There are no rigidly fixed limits of duration of normal bleeding. Some women attach considerable significance to the fact that their menstrual periods last a short time. They seem to believe that they must rid themselves of a required amount of toxic material at this time and, when their periods are of short duration, they infer that there has been incomplete menstrual purification. Prolonged bleeding need not be excessive. Prolonged bleeding may result from local disease of the uterus and endometrium, as polyp, fibromyoma or carcinoma. It may result from irregular shedding of the endometrium. On the other hand, it may be functional and may result from a failure of the normal hemostatic mechanism and conse-

quential teetering of estrogen levels at critical points which are insufficient to initiate a new phase of endometrial growth.

Abnormal Amount of Bleeding.—There is considerable variation in the amount of blood lost by normal women. Scanty bleeding per se is of no clinical significance. It may occur, however, in conjunction with debilitating constitutional diseases.

Prolonged bleeding or bleeding of normal duration may be excessive in amount. Uterine hemorrhage, as hemorrhage from any other site, may constitute a grave emergency. It may result from organic disease of the uterus and endometrium. It may be caused by functional disturbances characterized by teetering of critically low estrogen levels. Prolonged or excessive bleeding may or may not be associated with qualitative changes in ovarian function. Excessive bleeding which is associated with a progestational endometrium usually can be explained upon the basis of organic, endometrial or uterine disease. Clots frequently are passed when the bleeding is brisk. They have no particular significance save indication of a brisk hemorrhage which has resulted in nonliquefaction of the clot while the blood was still in the uterus.

Endometriums from Which Bleeding Occurs.—Bleeding of any duration and any amount may occur from any type of endometrium. Accordingly, the likelihood of a grave hemorrhage cannot be prognosticated by endometrial studies. Practically all the fatal functional uterine hemorrhages have occurred from poorly proliferated or atrophic endometriums. Hyperplasia of the endometrium is associated fairly frequently with hemorrhages during anovulatory cycles. The hyperplasia may result from excessive estrogen stimulation of endometrium, from prolonged estrogen stimulation, or from the accumulation of endometrium from several cycles, since the estrogen endometrium is not shed as completely as the progestational endometrium. Fairly cyclic bleeding, on the other hand, may occur from all types of endometriums. Accordingly, there is little clinical difference between bleeding from the various types of endometriums, save that dysmenorrhea is associated almostly uniformly with bleeding from a progestational endometrium.

AMENORRHEA

The term "amenorrhea" is used variously in medical writings to include infrequent flowing as well as nonoccurrence of bleeding. In this discussion the term is used to denote no bleeding and intercurrent amenorrhea is diagnosed when at least one year has elapsed without bleeding. The physiologic abeyance of bleeding incidental to pregnancy and the puerperium is not discussed.

Amenorrhea is classified as (1) physiologic, (2) hypo- or apubescent, and (3) intercurrent.

Physiologic Amenorrhea.—The absence of bleeding is physiologic prior to menarche and after the menopause. Premature menarche

(pubertas praecox) may be due to constitutional factors or to endocrine disease, as ovarian tumors, adrenal disease or hypothalamic disturbances. Premature menopause may be due to constitutional factors, pelvic surgery, irradiational therapy or premature senility of the ovary. Postmenopausal amenorrhea may be complicated by flowing due to endometrial malignancy, malignancy elsewhere in the generative tract, ovarian tumors, or overtreatment with estrogens. Premenarchal amenorrhea is characterized physiologically by hypogonadotropuria, whereas postmenopausal amenorrhea is associated with hypergonadotropuria.

Hypo- or Apubescent Amenorrhea.—Failure of menarche to occur at the usual age may be associated with hypopubescence (deficient sexual maturation) or apubescence (absence of any sexual maturation). Hypopubescent amenorrhea, prior to 18 years of age, may be a simple tardiness, which is corrected spontaneously. If menarche has not occurred by 18 years of age, however, hypopubescent amenorrhea likely is due to constitutional or endocrine disease. Apubescent amenorrhea rather uniformly is due to constitutional or endocrine disease.

Hypergonadotropuric apubescence is of grave prognosis for the initiation of normal ovarian cycles. Indeed, it represents a severe grade of intrinsic ovarian failure due to maldevelopment of the ovaries during the fetal period. These patients have been described as having a "premenarchal climacteric," since their hypergonadotropuria and their intrinsic ovarian failure are of the same order as those of climacteric women. Fairly satisfactory substitutional therapy with estrogens may be carried out but this therapy is not curative, and the responses to this therapy often are not completely satisfactory. These patients, therefore, must accept a state of hopeless sterility.

Amenorrhea associated with essentially normal sexual maturation should be differentiated from hypopubescent amenorrhea. Embryologic faults in development of the uterus may impair the functions of this end organ and, thereby, cause amenorrhea, despite the normalness of hormonal stimuli and the adequacy of function of the endocrine system in general.

Intercurrent Amenorrhea.—Postmenarchal, or intercurrent, amenorrhea may be due to diverse causes, as environmental or climactic alterations, emotional crises or neuropsychiatric disease, metabolic disturbances, constitutional or endocrine disease, pelvic surgery, irradiational therapy involving the pelvic organs, premature senility of the ovaries, ovarian tumors, (pregnancy and puerperium), or rarely functional disturbances. It may be transient, and be followed by a spontaneous recovery of normal function, or it may be absolute and final, and not always salvageable by intensive therapy. It may be associated with hypoestrogenism (low estrogen values), euestrogenism (normal estrogen values), or hyperestrogenism (elevated estrogen values) and, accordingly, sexual regressions occur only when there is associated

hypoestrogenism. It may be characterized by hypogonadotropuria (decreased urinary excretion of gonadotropins), eugonadotropuria (normal urinary excretion of gonadotropins), or hypergonadotropuria (increased urinary excretion of gonadotropins), depending upon its etiology, namely, deficient gonadotropic activity of the pituitary, diverse other causes, or intrinsic ovarian failure. It may be associated with virilization, due to ovarian tumors, as arrhenoblastoma, or adrenal rest cell tumor, or luteoma, or due to adrenal disease, as hyperplasia, adenoma or carcinoma, or due to intensive androgen therapy.

The clinical significance of amenorrhea depends upon its etiology. When constitutional or endocrine disease, metabolic disturbances, gynecologic disease and neuropsychopathy do not exist, the only significance of amenorrhea may be an undesired sterility or a disturbed psychosomatics. Amenorrhea is not incompatible with good health. The treatment of amenorrhea is conditioned by its etiology.

TREATMENT

Any discussion of treatment should emphasize that irregularities of uterine bleeding may be vagaries of normal menstrual physiology or symptoms of diverse diseases or disturbances of function. No irregularity of bleeding is a disease per se. Treatment is discussed according to clinical significance rather than from the standpoint of every irregularity of flowing.

Uterine Hemorrhage.—The term "uterine hemorrhage" indicates excesses of flowing, either prolonged or of usual duration, which cause increased blood loss with hematopoietic drain. When there is active hemorrhage or a history of past excesses, the immediate therapeutic objective is to stop the flowing or to forestall further hemorrhage. The next objective, unless gynecologic disease prevents, is the restoration of normal ovarian cycles. Uterine hemorrhage due to gynecologic disease, endocrine disease and medical illness will be discussed later. Our present consideration deals with functional uterine hemorrhage.

Most functional uterine hemorrhages result from critical teetering of estrogen levels and failure of the normal midmenstrual upswing in these values which is designed to check bleeding by initiating another wave of endometrial growth. As a rule, this break in normal physiology is related to episodes of hyporeactivity of the ovaries to pituitary gonadotropic stimuli. Accordingly, if this thesis be true, these episodes of bleeding can be stopped by raising estrogen levels by estrogen therapy. As a rule, it takes several days to secure "estrogen hemostasis." When the hemorrhage is grave, a more rapid form of hemostasis is necessary. This can be secured by curettage and, if necessary, a light packing of the uterus and vagina. When a patient is thirty-five years of age or older, hemostasis should be secured by curettage, rather than by estrogen therapy, since it is obligatory to exclude the possibility of malignancy of the endometrium.

There is no need to give estrogens by injection. All of our estrogen therapy is oral. We prefer natural estrogens in general and in particular when functional uterine hemorrhage is treated. The natural estrogen of our choice is a commercial preparation of conjugated estrogens, "premarin," which is chiefly estrone sulfate. The usual dosage of premarin which we employ for hemostasis is 7.5 mg. per day. (Premarin is available in tablets of 1.25 and 2.5 mg.) If bleeding has not decreased significantly by the third day of treatment, the dosage of premarin is increased by 50 or 100 per cent. Usually there is little difficulty in securing hemostasis within three to five days.

Hemostasis, whether secured by curettage or by estrogen therapy, is only the beginning of treatment. If estrogen therapy is discontinued when the patient ceases to bleed, there will be a return of bleeding (withdrawal bleeding) within three to five days. Bleeding usually returns relatively promptly if no treatment follows curettage. Accordingly, the daily dosage of estrogen which was required for hemostasis is continued for twenty days, in order to assure at least twenty days without bleeding. During the last ten of the twenty days of estrogen treatment, oral progestin (anhydrohydroxyprogesterone) is given. The dosage of oral progestin is arbitrary: for each 1.25 mg.-unit of premarin we use 10 mg. of oral progestin. When this treatment is concluded, withdrawal bleeding results usually within three to five days.

When hemostasis has been secured by curettage, we employ similar cyclic estrogen-progestin treatment but use a lower dosage. Within three to five days after the curettage, treatment is started and the patient is given 3.75 mg. of premarin daily for twenty days; during the last ten days of this twenty days of estrogen treatment, the patient also receives 30 mg. of oral progestin daily.

On the third day of flowing following the first series of cyclic estrogen-progestin therapy, another cycle of treatment is initiated and it is given in a similar fashion, employing the same dosage schedule, in most instances, as that which followed curettage hemostasis. In all, three or four cycles of estrogen-progestin therapy are given. At times, it may be necessary to elevate the dosage of therapy, as when "breakthrough" bleeding occurs.

By carrying out this estrogen-progestin substitutional therapy, the patient is assured cyclic bleeding of normal amount. In the majority of patients, this therapy, by resting overstimulated ovaries and by reordering reciprocities of the ovary, pituitary and endometrium, facilitates a return of normal ovarian cycles. This fact can be ascertained from studies of basal temperature graphs or from studies of endometrial biopsy tissue secured at the onset of episodes of bleeding, following discontinuation of treatment.

If there is not a return of normal ovarian function, we give several additional cycles of estrogen-progestin therapy in which the dosage of progestin is increased. The treatment formula for these cycles is this;

premarin is given as previously described, 3.75 mg. daily for twenty days; during the last ten days of this twenty days of estrogen therapy, 25 mg. of progesterone is given intramuscularly every other day.

There is no reason to hesitate to employ estrogen-progestin therapy in the treatment of functional uterine hemorrhage of premenopausal women. It is preferable to irradiation therapy, which may mask an early malignancy of the endometrium, which was overlooked during the initial curettage. The false security which results from irradiation may contribute to a costly delay in the recognition and proper treatment of the condition. The hormonal therapy which has been described does not impair the endometrium's ability to serve as an indicator of local disease. Estrogen and progestin, when they are given according to the schedule described, are not carcinogenic.

Impaired Fertility.—Treatment of impaired fertility associated with functional excesses of bleeding has been discussed. Prior to continuing this discussion, these observations are warranted. Ovarian sterility constitutes a minor cause of childlessness. It is encountered in less than 5 per cent of wives of childless couples. Furthermore, the problem of sterility should be approached broadly with an investigation of adequate scope of both members of the couple.

The reduction in fertility which is incident to infrequent but ovulatory cycles requires no treatment, save instruction of the woman in taking basal temperatures so that she may recognize and act upon ovulation. Endocrine therapy, with the exception of desiccated thyroid gland for hypothyroidism, is apt to disturb the quality of ovarian function, rather than increase the number of ovulatory cycles. When rapid gains of weight are responsible for infrequent cycles, loss of weight by reduction diets usually improves the chronology of the cycle.

The hopeless prognosis of hypergonadotropuric apubescence has been mentioned. The hypoplastic ovaries of these individuals cannot be stimulated to initiate normal and spontaneous functions.

A similar prognosis may be given the woman with premature menopause, that is, postmenarchal or intercurrent hypergonadotropuric amenorrhea.

When hypogonadotropuria or eugonadotropuria characterize hypopubescence and intercurrent amenorrhea, a trial of gonadotropic therapy may be carried out. Unfortunately, even in patients with hypogonadotropuria, this therapy commonly is ineffective. Making use of the best gonadotropins available commercially, we have described what was called "one-two cyclic gonadotropic therapy," which is designed as a quantitative and qualitative substitution for cyclic pituitary function. This therapeutic schedule has proved of value in some women with anovulatory cycles. It may be tried in amenorrhea. It is summarized.

Equine gonadotropin (from the serum of the pregnant mare) and chorionic gonadotropin (from human pregnancy urine) are given in

sequence and by intramuscular injection. The patient should be skin tested with a preparation of equine gonadotropin before each series of treatments, because of its frequent allergic characteristics. If there is no allergy the first trial cycle is initiated and the results of treatment are gauged by basal temperature studies and by endometrial biopsy, if bleeding follows. For ten consecutive days, the patient receives daily intramuscular injections of 500 international units of equine gonadotropin. Immediately following this, the patient receives for ten days daily intramuscular injections of 500 I.U. of chorionic gonadotropin. If basal temperature data or endometrial biopsy data indicate that ovulation was induced, cycles of this treatment are given every three months in conjunction with trials at pregnancy, which are calibrated with thermic evidence of ovulation.

If there is no evidence that this treatment has stimulated the ovaries, it may be repeated after an interval of three months or more, and following a negative skin test with the preparation of equine gonadotropin. This second trial of therapy is given similarly as the first, save that the daily dosages of both gonadotropins are doubled. If no evidence of ovarian stimulation is secured from the second trial of treatment, a third trial of treatment may be made similarly after a rest interval of three months or more. This trial of treatment may employ daily doses which are three or four times the initial dosage. If this trial gives negative results, there is no need for further trials of gonadotropic therapy.

There is relatively little difficulty in producing withdrawal bleeding in amenorrheic patients following cyclic estrogen or cyclic estrogen-progestin therapy. This bleeding is artificial and should not be construed as resulting from any stimulation of ovarian function. Recent publications have manifest some enthusiasm for the results secured in the treatment of amenorrhea with relatively large dosages of progestin. In fact, a number of commercial preparations of estrogen and progestin is being offered for the so-called "short treatment" of amenorrhea. Our results with this treatment do not indicate that it represents any significant contribution to the cure of the ovarian failure responsible for the amenorrhea. It may be tried. This plan of trial is suggested:

For twenty days the patient is given 3.75 mg. of premarin by mouth daily. During the last ten days of this twenty days of estrogen treatment, 25 mg. of progesterone is given intramuscularly every other day. This treatment is continued for two additional cycles, each cycle of treatment being initiated at the end of withdrawal bleeding. After three cycles of this treatment, an inventory of salvage is taken by studies of basal temperature values and by endometrial biopsies at the onset of bleeding, if the patient bleeds. Most of our patients do not bleed when treatment is discontinued.

In general it may be said that little can be done to accomplish the return of normal spontaneous ovarian cycles in patients with amenor-

rhea unless the amenorrhea is due to medical disease which can be cured or improved, or due to endocrine disease, as hypothyroidism, diabetes mellitus, which may be improved by specific treatment, or due to metabolic disturbances which may be corrected, or due to other extra-endocrine conditions which may be eradicated or improved. Some clinicians report good results from so-called "low dosage irradiation" of the pituitary and ovaries. Others describe return of normal ovarian cycles following "wedge resection" of cystic ovaries. We have not practiced these methods.

The so-called "one-two cyclic gonadotropic therapy" should be tried in patients with anovulatory cycles and undesired sterility. Success has attended this therapy in a number of women, investigated and treated by us because of childlessness.

Psychosomatic Disturbances.—At times it may seem expedient, if not necessary, to treat various psychosomatic disturbances related by the patient to infrequent ovarian cycles or to scanty uterine bleeding. The pressure for this treatment may come from the patient herself or it may come from her neuropsychiatrist or her internist. At other times it may result from an endogenous conviction that endocrine treatment is the easiest way around a difficult problem or that endocrine treatment is cheaper for the patient than prolonged psychotherapy. For this form of treatment, the following schedule is suggested:

The estrogen should be given orally. For example, we suggest 1.25 or 2.5 mg. of premarin daily for twenty days. Treatment should be started on the fifth day of the cycle (five days after the onset of bleeding). Treatment should be resumed at the same time following withdrawal bleeding. Individual circumstances will determine how many cycles of treatment are necessary or advisable. It should be cautioned that this form of treatment most likely will upset the quality of ovarian function if the patient is having normal ovulatory cycles. When treatment is discontinued, normal cycles may or may not be resumed.

It may be mentioned that the cyclic use of estrogen therapy, as just described, in the treatment of dysmenorrhea is common, and apparently helpful. It probably falls under the classification of psychosomatic therapy. It has been our general experience that no permanent damage to the quality of ovarian function results from this cyclic estrogen therapy.

The use of estrogens in the treatment of severe symptomatic disturbances, incidental to the climacteric, warrants inclusion in this discussion. The purpose of estrogen therapy at this time is not to regulate the cycles of bleeding but to decrease the subjective distress. When estrogen therapy of premenopausal women is necessary, the administration of estrogens should be calibrated with their bleeding cycles, in order to avoid irregularities of bleeding. Furthermore, treatment at this time should not employ full substitutional dosages of estrogens or should not be continued unduly long lest the process of

the climacteric be delayed. Acyclic administration of estrogens, at varying intervals and in large dosages, at this time of life, constitutes an ideal formula for keeping the endocrine system in a state of chaos and flux.

When it is necessary to treat subjective symptomatology in the postmenopausal woman, estrogen dosage should be kept particularly low, lest there be undue endometrial stimulation and ultimate withdrawal bleeding. Estrogen therapy at this time should be given cyclically and the formula which we suggest is twenty days of treatment followed by a withdrawal of treatment for ten days. We do not believe that the daily dosage of estrogen at this time should exceed 0.625 milligrams of premarin. Even this small dosage, if continued for many cycles, may be followed by withdrawal bleeding. Withdrawal bleeding in the postmenopausal woman, even though it may be correlated with antecedent estrogen therapy, always poses the possibility of endometrial malignancy and frequently leads to a diagnostic curettage.

Organic Diseases, Endocrinopathies and Gynecologic Conditions.— One of the chief, if not the foremost, significancies of irregularities of bleeding is the likelihood that they may be symptoms of a disease, which should be diagnosed and appropriately treated. Any therapeutic approach which ignores this fact and which considers a functional disturbance without ruling out these conditions, is a hazardous one. It is obviously impractical, and not necessary, to attempt a detailed discussion of all the diseases which may result in irregularities of bleeding. This general statement appears to be in order: When gynecologic surgery or pelvic irradiation is being considered, due consideration should be given to restoration or preservation of normal ovarian function, if possible; there is entirely too much unnecessary destruction of function by both of these therapeutic approaches. A gynecologist, or a surgeon, who thinks in terms of ovarian function and in terms of fertility, rarely does unnecessary removals of genital organs.

FERTILITY IN MEN

E. Perry McCullagh, M.D., F.A.C.P.*

GENERAL CONSIDERATIONS

Only in the past few years has anything but the most cursory attention been given to the study of fertility in men. A great deal has been done from the embryologic and histologic points of view, and a moderate amount of knowledge regarding endocrine and nutritional aspects has been acquired in work with the experimental animal and in animal breeding. The greatest lag has been in the application of available knowledge to the human and the development of more accurate means of diagnosis and treatment. Progress is now being made, and sterility clinics are being operated by many of the larger hospitals and clinics.

It is generally accepted that in a study of childlessness a careful examination of the semen is always necessary, and, in addition to evaluation of the general health of the husband, such values as testicular biopsies and hormone assays may be needed.

Some of the more important clinical facts will be mentioned.

The approach to the patient varies considerably and requires judgment and understanding on the part of the physician. Frequently the wife comes alone to inquire regarding the cause of childlessness. More frequently in recent years both husband and wife appear, psychologically prepared by their own physician to undergo whatever examinations are required.

Occasionally a single man wishes an estimate of fertility in anticipation of marriage or for other reasons, sometimes because of a fear of damage from previous venereal infections or to corroborate or refute opinions obtained elsewhere. An examination of the semen is requested as the first step in the investigation. If this is normal, physical examination and further tests on both partners may be in order.

In most cases, necessary examinations are readily arranged, but occasionally an impasse is reached in which the wife refuses to request semen examination for fear of the ill effects which psychological factors might produce on the husband or because of actual refusal of the husband to appear or to submit semen for examination.

HISTORY

A careful history may supply important leads as to the cause of infertility. Facts such as the following should be elicited with care.

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The history of development of the genitalia, time of puberty and the possibility of cryptorchidism in the past should be investigated. A history of excessive obesity in childhood may suggest adiposogenital dystrophy from which complete recovery may not have occurred. Early severe infections or fevers, especially mumps, is important. A careful history of nutrition may be of importance. The possible harmful effects of vitamin A and B deficiency and the lasting effects of vitamin E deficiency in animals should be kept in mind, though their true relationship to human fertility is not yet clear.

During adult life possible effects from toxic or infectious agents and endocrine or metabolic disease should be considered. The occupation may be of importance; possible exposure to heavy metals or to x-ray and suggestive evidence of pituitary, thyroid or adrenal disease and diabetes should be examined. Local damage may have occurred as the result of surgery, rarely trauma. Injury to the ducts as the result of gonorrheal epididymitis is common. Prostatitis may be a factor, though this is apparently unusual and considerable chronic prostatitis is not necessarily inconsistent with fertility. A history of urethral instrumentation or posterior urethral cautery or surgery may be significant.

Sexual history should never be taken for granted, even in apparently normal, well educated men. Detailed inquiry should be made into the normality of the sexual act and the frequency of coitus, bearing in mind that too infrequent relations reduce chances of the sperm's reaching the ovum, while intercourse as often as daily or alternate days may materially reduce the sperm count. It may be illuminating to inquire regarding fertility in a previous marriage or information obtained from former physical and semen examinations.

The age of the patient, the number of years married, and the fertility history of the wife are all matters of importance. The possible harmful effects of immediate semen loss from the vagina or the inadvertent use of precoital or postcoital douches need consideration.

Psychologic factors such as worries connected with occupation, anxiety regarding sexual normality, or other reasons may be important, and chronic fatigue is not conducive to the highest grade of fertility for the individual in question.

PHYSICAL EXAMINATION

If the semen examination is normal the physical examination of the patient is perhaps less important than in the presence of abnormalities. It is wise, nevertheless, to bear in mind that minor abnormalities in the semen may not be evident with the methods available at present, and the general health of the individual is therefore still an important factor. As in all physical examinations certain laboratory tests probably should be considered routine. These include urinalysis, Wassermann tests, blood counts and blood sugar estimation, and it is well to add basal metabolic rate. The physical examination should give special

consideration to gross abnormalities of body weight and signs of endocrine disorder, especially those relating to hypogonadism. A careful examination of the genitalia and accessory glands is necessary, paying particular attention to penile and testicular abnormalities and the prostatic fluid for signs of infection as well as further examination of urethral smears or urologic examination when any suggestive findings indicate the need for it.

SEMEN EXAMINATION

Examination of the semen and sperm may be considered under several headings:

1. Methods of obtaining the semen
   - (*a*) Masturbation
   - (*b*) Coitus interruptus
   - (*c*) Condom
   - (*d*) From the vagina
   - (*e*) Vesicular massage
2. Precautions in obtaining and transporting the specimen
3. Examination of the sperm obtained from other sources
   - (*a*) From the cervix
   - (*b*) From the uterus
   - (*c*) By testicular or epididymal aspiration
4. Technic of examination and the normal semen
5. Abnormalities associated with reduced fertility

Methods of Obtaining the Semen.—*Masturbation.*—The most practicable method of semen collection in many ways is the production of a specimen by masturbation at the office with ejaculation directly into a dry, clean, wide-mouthed glass container. When this method is used it has the advantage of delivery of the specimen to the laboratory at once and of being as certain as possible that the entire specimen is obtained and properly transported. It is not free, however, from disadvantages; religious or other ethical objections may be raised. The patient may object because of embarrassment or be actually unable to produce a specimen in this manner. There is also the objection which might be raised to other methods, namely that the semen must be examined after having been in an abnormal environment out of contact with the effects of normal secretions of the vagina and cervix. In addition, it is frequently the case that coitus has occurred within three days of the time the patient presents himself for examination. Ejaculation more frequent than this may result in a low sperm count. If normal semen is demonstrated in spite of recent ejaculation, no repetition is necessary. If the count is low the test should be repeated later.

Coitus Interruptus.—Clear instructions must be given in each case to insure as well as possible the obtaining of all the semen ejaculated and at as short a time as possible prior to its arrival in the laboratory. The ejaculate is passed directly into a wide-mouthed glass bottle.

Use of a Condom.—This is a very poor method and never advised by us. Immobility of the spermatozoa in a condom specimen can never be properly interpreted because normal sperm may be very short-lived in contact with the materials of the condom.

Recovery of Semen from the Vagina.—This method has not proved satisfactory because part is lost and most of the sperm is rendered immotile in the vaginal secretions. It may be interesting on occasions to compare these findings with those obtained on examination of a fresh specimen.

Examination of Sperm in Fluid Obtained by Prostatic and Seminal Vesicular Massage.—This is most unsatisfactory, since the sperms are stored almost entirely in the epididymis and what few sperms may be obtained by massage of the vesicles do not represent those which would be found in a normal ejaculate.

Precautions in Obtaining and Transporting the Specimen.—The time elapsed between previous ejaculation and the obtaining of the specimen should be three or more days. Long intervals of time are also undesirable. Some individuals with relative impotence under such circumstances as may exist, for example, in acromegaly may be able to supply a specimen only once a month. A relatively normal count only obtainable at such a long interval loses much of its meaning. An interval of four days is therefore advised for the sake of more accurate comparison with normal, and with individual changes.

The container should be dry and clean and should not be rewashed, as it may contain water which would interfere with the normality of the semen. We prefer to use a wide-mouthed, 1 ounce bottle with a plastic screw top rather than a rubber cork. Under no circumstances should the container be warmed nor should any attempt be made to keep it warm in transport. This seems to be a natural error and without warning patients will arrange in some way to warm the container before use or to carry it to the office under the clothing. The life of the sperm is distinctly shortened by heat, and since motility at present is judged at room temperature, a temperature of 70°F. or below is preferable for transport. Future studies may show that estimation of sperm motility at more carefully regulated temperatures in the laboratory may be desirable.

The container should be carefully labeled with the name and clinic number of the patient, the date, and the hour at which the specimen was obtained. It is well to question the patient regarding the completeness of the specimen, especially when less than 2 cc. of semen is delivered.

Examination of Sperm Obtained by Other Means.—*Sperm from the Cervix (Huhner Test*[1]*).*—This simple test was described in 1913 and is still in constant use. It consists of the recognition of live spermatozoa in the cervical mucus. The woman presents herself as soon as possible after coitus. The speculum is inserted without

lubrication, the cervix is wiped clean, and a small amount of cervical mucus obtained with a wire loop or cannula is examined at once. The finding of live sperm obviously gives much information as to the relative importance of abnormalities which might be theoretical barriers to fertility between the production of the semen and its entrance to the cervical canal.

Sperm from the Uterine Cavity.—Sperm may be obtained from the uterine cavity in the same manner as from the cervix. However, it is difficult to determine whether or not they have been introduced with the instruments or to obtain them with enough consistency to make the method useful.

Aspiration of the Testicle to Obtain Sperm.—This method was also advised by Huhner and has been employed to considerable advantage. If live sperm are seen, information of value is obtained, especially if none are in the ejaculate. Many of the sperm in testes are normally immotile or very slightly motile, however, so that with needle biopsy of the testes results are often equivocal. The method seems now to be largely replaced in most clinics by semen analysis and surgical biopsy of the testis. If an occlusion of the epididymis is suspected and it is known that there are no sperm in the semen but that there is normal spermatogenesis in the testes, the demonstration of normal spermatozoa in the epididymal head may indicate the possibility of a cure by vaso-epididymal anastomosis.

Technic of Semen Examination.—Semen examination involves a study of the specimen to determine appearance, volume, viscosity, pH, sperm count per cubic centimeter, and in total, estimate of the number of motile sperm, the degree of motility and the duration of motility (viability), presence and type of other cells and bacteria. Stained smears are also examined to determine the morphology of the sperms and to make an estimate of the immature, teratologic and degenerated forms present.

At times such features as the power to dissolve cervical mucus, hyaluronidase content, chemical analysis for fructose, or other constituents may be added, but such measurements as these as well as any metabolic studies of the sperm themselves are still matters chiefly for investigation rather than for clinical application.

All of the facts gained must be interpreted in the light of an intimate knowledge of the history and physical condition of the patient and the conditions under which the semen was obtained.

Technic of Semen Examination and Normal Values

Reagents:

1. Semen-diluting fluid: 5 gm. sodium bicarbonate, 1 cc. formalin and 100 cc. of distilled water are mixed thoroughly.
2. Buffered water: (pH 7.0) Prepared for use by mixing 61.1 cc. of anhydrous disodium phosphate M/15, 38.9 cc. sodium or potassium acid phosphate M/15, and 900 cc. distilled water.

3. Giemsa stain: 1 cc. Giemsa stock solution is mixed with 50 cc. of buffered water. This stain is made fresh every day.

Gross Examination.—This includes a measurement of the total volume to which is added 0.6 cc. to cover the loss of the specimen on the sides of the container. A volume of 2 to 6 cc. is considered normal. Volumes as high as 12 cc. have been seen. The average specimen is opaque, grayish in color, and shows a mild degree of viscosity. If lifted with a stirring rod, semen of average viscosity tends to string between the surface of the semen and the lifted rod. Sometimes highly viscous material is present in masses of varying size. A normal alkalinity of pH 7 to 9 is consistently found, greater variation is rare.

Microscopic Examination.—A full drop of the semen is protected with a cover slip and the following facts are noted:

1. *Motility of the Sperm.*—The semen should not be examined for sperm motility until at least one-half hour after ejaculation so that there is no impediment to motility by incompleteness of liquefaction. A fertile specimen presents a field teaming with actively motile sperm. Familiarity with the picture enables one to grade the activity and judge the percentage of motile cells.

There is no thoroughly satisfactory method of making the estimation. A relatively accurate means has been recommended by Hotchkiss:[2]

"The percentage of motile cells is estimated by placing a disk in the ocular (of the microscope) with one quarter area cut out. This can easily be done by cutting out a round piece of black paper which will slip on the ring within the chamber of the ocular. For accurate estimations the number of motile cells is counted in the quarter field when viewed for ten seconds. All of the cells, active and inactive, within the same field are then counted. Each number is multiplied by 4 to determine the number present in the entire microscopic field. The percentage of motile cells is easily computed by assigning the number of motile cells as the numerator and the total cells as the denominator."

The degree of motility is expressed in terms of 0, 1+, 2+, 3+, or 4+. Thus the report contains a statement such as 1 hr., motility 80%, 3+.

In a normal specimen we may expect 3 plus to 4 plus motility of 70 to 80 per cent of the sperm one hour after ejaculation. At room temperature a specimen three to four hours old should show 50 per cent or more spermatozoa with active progressive movement. The visibility, which is noted four to five hours after collection of the specimen, should show little reduction in the activity of the sperm at room temperature, and normally some motility may be expected after as long as twenty-four hours. Additional notation is made of the following:

2. *Presence and number of epithelial cells.*
3. *Presence or absence of white and red blood cells.*
4. *Any type of crystal formation.*
5. *Bacterial contamination.*

In our own series, 500 consecutive semen examinations from child-

less families were taken as a total sample for analysis. From these, 100 patients were selected in whom the childlessness was explainable on the basis of abnormalities found in the wife and no apparent abnormality was present in the husband. Tests in the wives included vaginal smears, estimation of cervical pH, tubal patency tests and endometrial biopsies.

For comparison 200 others were selected in which no abnormality was found in the wife. In ninety of the 100 "normal" husbands 4 plus motility was found in semen one-half to three hours old in over 60 per cent of the sperm present. In the "abnormal" husbands judged on this basis, sperm motility of the type mentioned was present in only twenty of the 200 men in question, or 10 per cent.

Counting Technic.—The specimen is thoroughly mixed, and a 1:20 dilution with semen-diluting fluid is made in a white blood counting

TABLE 1

NORMAL VALUES IN SEMEN EXAMINATION AS FOUND BY VARIOUS INVESTIGATORS

Author	Amount (Volume)	Motility (Per cent)	Count	Percentage of Normal Forms
Weisman	2.5–5 cc.	70	100,000,000	85
Meaker	3–6 cc.	70	100,000,000	85
Cary	3.5 cc.	60	60–100,000,000	80
Lane-Roberts	1.5–6 cc.	?	50,000,000	82
Mazer and Israel	4 cc.	90	100,000,000	80
William and Simmons	2–6 cc.	60	50–60,000,000	78
Pollak	3–5 cc.	75–80	60–120,000,000	70–80
Hamblen	3–4 cc.	80–95	60–120,000,000	80
McLane	3–3.5 cc.	60–70	60–120,000,000	75
Hotchkiss and MacLeon	3–4 cc.	50	100,000,000	80

(Reprinted from Conference on Diagnosis in Sterility, ed. by E. T. Engle. Springfield, Charles C Thomas, 1946, p. 17.)

pipette. The counting chamber is filled, and the sperm are counted in the same manner as red blood cells. To compute the number of cells per cubic centimeter this number is multiplied by 1,000,000. The number of sperm in the ejaculate is found by multiplying by the total volume. The normal values vary greatly; however, 1 cc. of the specimen should contain between 50,000,000 and 100,000,000 spermatozoa (Table 1). In our "normal" husbands in childless families mentioned above, counts of over 50,000,000 per cc. were present in 87 per cent of the men.

Morphology of the Spermatozoa.—A thin smear of the seminal fluid is made and allowed to dry. Debris is removed from the slide by rinsing first in semen-diluting fluid and then in buffered water. The preparation is stained for twenty minutes in Giemsa's stain and counterstained for one second with carbol fuchsin. This method of staining

permits illustration of the head, midsection, and tail of the sperm. Other methods of staining are outlined by Hotchkiss. The percentage of normal and abnormal cells can then be computed easily. In our "normal" husbands mentioned above more than 18 per cent abnormal forms were present in only 5 per cent of the men. In the "abnormal" husbands over 18 per cent abnormal forms were present in 27 per cent of the men.

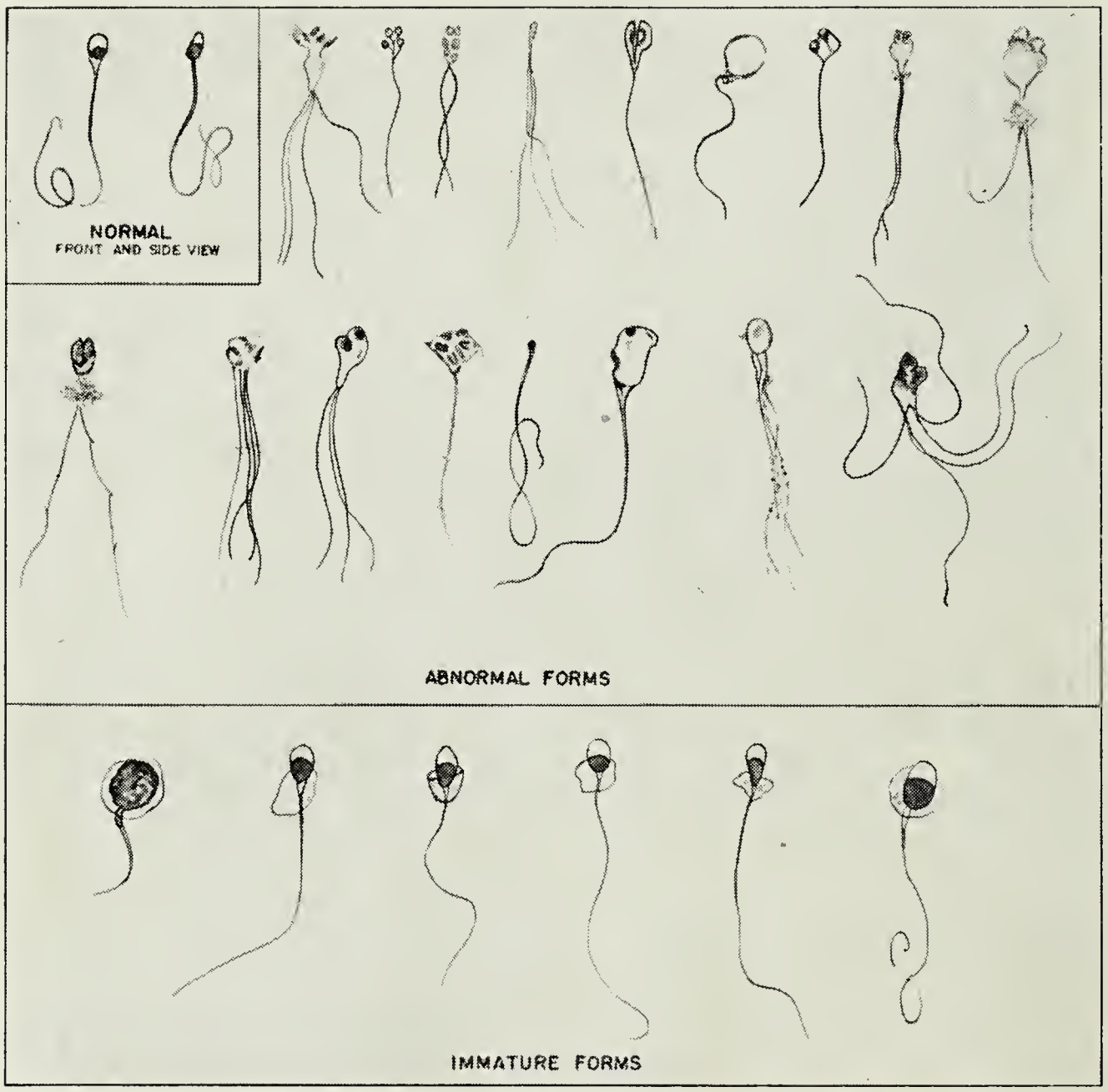

Fig. 21a.—Normal, abnormal and immature forms of spermatozoa.

Types of Abnormal Forms:

1. Degenerate: granular degeneration of the cytoplasm, fragmented nucleus (head).
2. Immature: usually recognized by cytoplasm attached below the head.
3. Teratologic: multiple heads, pin heads, large heads, multiple tails.

Abnormalities Related to Diminished Fertility

Fertility is diminished by specimens of abnormally low volume. It is also possible that specimens of very high volume may be impaired in fertility from the fact that the sperm count, though normal in total, is

low per cubic centimeter due to dilution. If this proves to be the only abnormality in a childless couple, concentration of the sperm by centrifugation and artificial insemination might be a worth-while consideration.

In some specimens addition of hyaluronidase plus centrifugation will produce a concentration of the sperm. For example, one specimen tested in this way showed on the first count 64,000,000 sperm per cc., 30 per cent of which were 4 plus motile in one hour. After centrifugation the fluid near the bottom of the tube contained 308,000,000 sperm per cc. When hyaluronidase was added and part of the specimen centrifuged the count rose to 528,000,000 per cc. Whether this method will prove useful as a means of increasing the value of specimens for artificial insemination remains to be determined by further experience.

It is generally accepted that sperm counts below 50,000,000 per cc., less than 60 per cent motile sperm, and with more than 20 per cent abnormal forms have impaired fertility. Pregnancy occasionally occurs when the husband's sperm count is lower than this. One of my patients had sperm counts ranging from 15.3 to 66 million. The motility was 3 to 4 plus in 60 per cent in one hour. During treatment with pituitary gonadotrophin there was a reduction of abnormal forms from 36 per cent to less than 17 per cent, but no other improvement in the semen was noted. The wife became pregnant and was delivered of a normal child. A count done ten days after the calculated date of pregnancy was only 18,300,000. The semen changes were so slight that the result scarcely seems to be ascribable to the treatment. Such experience demonstrates the difficulty of honest evaluation of such therapy and probably should be considered merely to emphasize the fact that relatively infertile husbands may have children if they have highly fertile wives.

TESTICULAR BIOPSY

A recent method in the investigation of testicular function is testicular biopsy. The older methods of testicular aspiration or punch biopsy of the testes having proved completely inadequate, these have been replaced by surgical biopsy of the testes. The procedure is simple and does not require hospitalization. It may be done with local or preferably under very short general anesthesia. The experience cited here is limited to surgical testis biopsies, the punch biopsy method having been discarded some years ago. Almost all of these have been done on our patients by Dr. C. C. Higgins. A small incision is placed in the scrotum, a small or angled incision is carried through the tunica albuginea, the testis is squeezed, and the small amount of extruding testis tissue 1 to 2 mm. in diameter is grasped with iris forceps and snipped out with fine scissors. The incision in the tunica need not be sutured; catgut is used in the skin so that no subsequent removal of sutures is necessary. Both testes are biopsied if possible. No complications have been seen in any of the several hundred biopsies done in

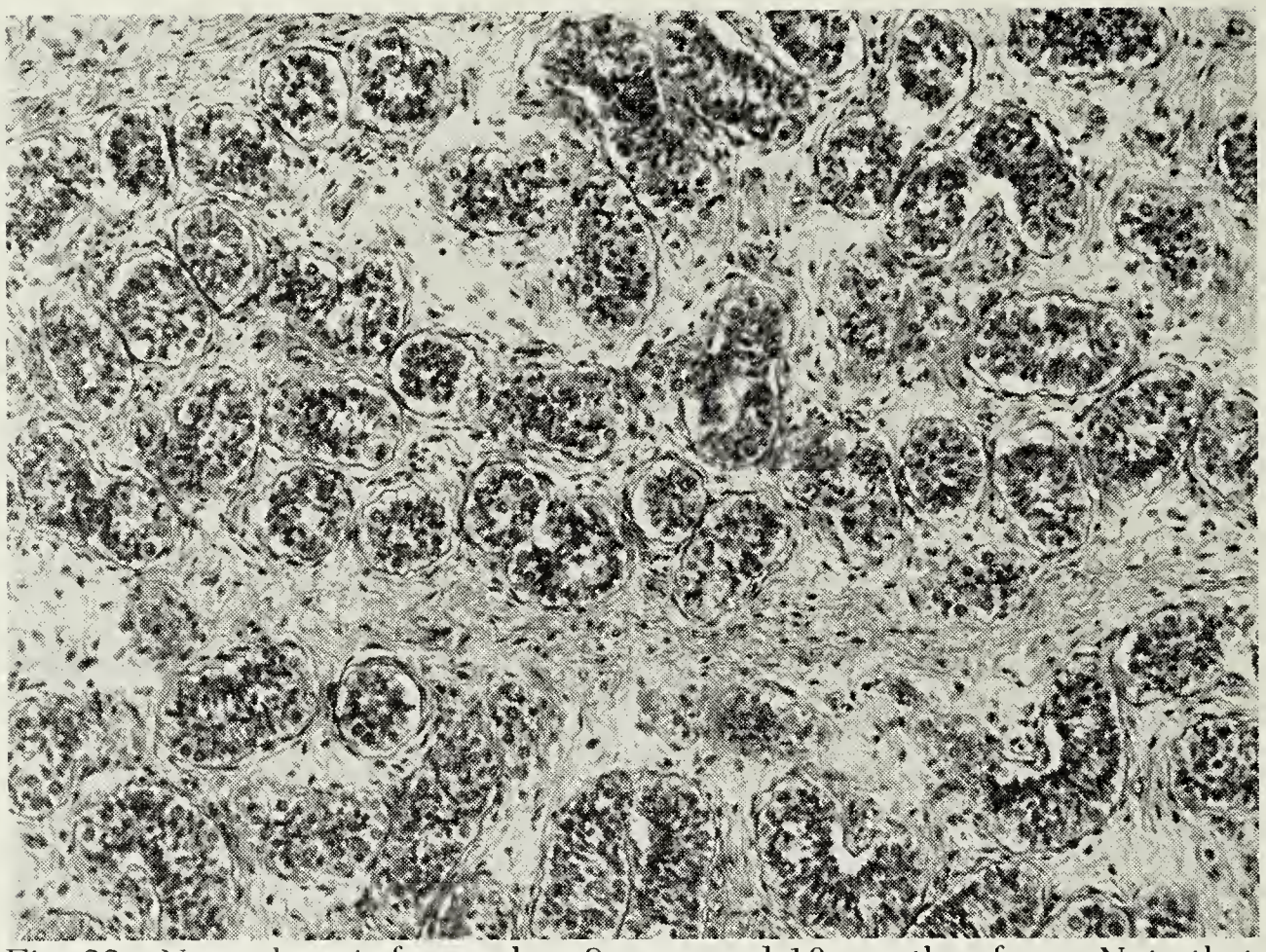

Fig. 22.—Normal testis from a boy 8 years and 10 months of age. Note that the tubules are generally represented by solid cords, though a few small lumina may be seen. They are comprised generally of relatively small, dark staining cells with little cytoplasm. In the majority of the tubules there are several round cells, that are acidophilic rather than basophilic and measure 12 to 15 microns. The basement membrane is relatively thin and islands of Leydig cells are not apparent.

Fig. 23.—Normal testis from a man aged 36 years. Vasectomy had been done 11 years previously. The gland not only demonstrates the normal mature testis tissue but serves as an example that vasectomy does not destroy tubular function.

my patients. Hematocele is known to occur. Normal testicular structure is shown in Figures 22 and 23.

An excellent survey of the present status of this procedure is that of Charney.[3] In a survey of biopsies on 308 patients he found normal spermatogenesis in forty-five. Of the remaining 263 patients there were developmental lesions in 18 per cent, degenerative lesions in 46 per cent, inflammatory lesions in 36 per cent.

The developmental lesions vary from complete absence of spermatogenic elements, in which no testis tissue is recognizable through

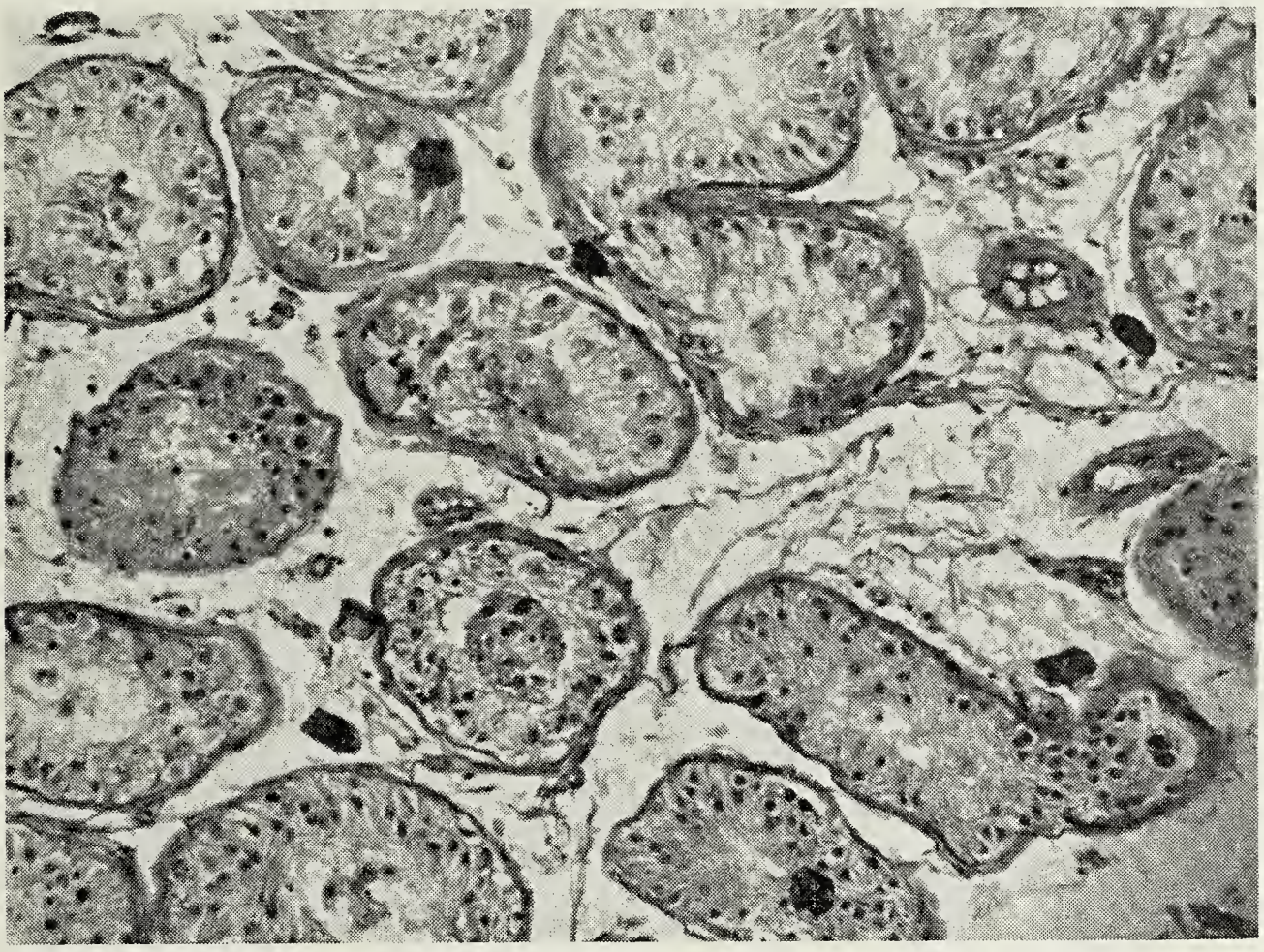

Fig. 24.—Testis biopsy in a youth aged 18, height 66 inches, weight 156 pounds. Clinical diagnosis: adiposogenital dystrophy. There was no history of mumps or any orchitis. Urinary 17-ketosteroids 8.8 mg. F. S. H. less than 105 m.u./24 hours. The tubules are hypoplastic and the basement membrane is thickened. Occasional spermatids and sperm heads may be seen. Some tubules contain a few spermatogonia and spermatocytes, others consist almost exclusively of Sertoli cells. In many cases of this type, high urinary gonadotrophins are present.

those in which the tubule contains only a mass of Sertoli cells (Fig. 24) to changes in which primary but no secondary spermatocytes or spermatids are seen and borderline cases in which very mild degrees of arrested development are judged to be present. It is a remarkable sight to view the testes of a man with azoospermia and find a structure which appears normal in all respects except for slight spermatocyte disarrangement and absence of the last stage of maturity of the spermatids (Fig. 25). In some such instances many spermatids are present in the majority of the tubules but not a single mature spermatozoon is to be found. In such patients who have had a diagnosis of

adiposogenital dystrophy in adolescence, apparent anatomic improvement may have occurred, yet the semen may remain abnormal. In most of these the tubule is smaller than normal, the interstitial elements appear relatively abundant in comparison, and thickening of the basement membrane may form a slight to an extreme change.

Degenerative changes such as occur in various types of toxemia, vascular disturbances or pituitary deficiency also show great variety. In milder changes there is a suggestion of tubular shrinkage, various degrees of degeneration of the tubular elements with an increase in

Fig 25.—Testis from a man aged 31 with azoospermia. Urinary 17-ketosteroids 10 mg., androgen assay, capon, 37 I. U., urinary F. S. H. 212 to 318 m.u./24 hrs. The remarkable feature of this biopsy was that there are many spermatogonia, spermatocytes, some spermatids but no spermatozoa. A few tubules are comprised largely of Sertoli cells. The Leydig cells appear normal.

intratubular cellular debris, swelling and vacuolization of the other spermatogenic elements. In many instances we have seen relatively normal testicular tissue in the presence of acromegaly. In Simond's disease, however, extreme fibrosis may be present with almost complete disappearance of tubular elements.

Inflammatory changes may be associated with signs of acute inflammation together with necrosis of the tubular elements or evidence of specific disease such as tuberculosis. More chronic changes are indicated by progressive thickening of the basement membrane to such an extreme degree that it may occupy more space than the remainder of the tubule. In some the degeneration of tubular elements advances to

a point where most of the tubular tissue assumes an appearance of hyalinization. Such changes may be the end stage result of mumps orchitis (Fig. 26).

Fig. 26.—Testis biopsy in a man aged 24, weight 170 pounds, with prepuberal hypogonadism with gynecomastia. Urinary 17-ketosteroids 12.6 mg./24 hrs., although it is evident clinically that the androgens are low. Urinary F. S. H. 212 to 318 m.u./24 hrs. The testicular changes are apparently the result of mumps orchitis at the age of 8 years. The extreme fibrosis and the sclerosis of the tubules and the fact that those containing cell outlines are apparently remains of Sertoli cells is evident.

TREATMENT OF STERILITY IN MEN

If several semen examinations show complete azoospermia and testicular biopsy reveals complete aspermocytogenesis, it may be prudent to abandon any plan of treatment of the husband. In instances of severe oligospermia or aspermia where testicular biopsy indicates normal spermatogenesis, relief of the obstruction may be considered. If this has been due to severe trauma or surgical injury to the ducts within the prostate or to congenital absence on part of the duct system, such means will probably be impracticable. If the obstruction is due to gonorrheal epididymitis and its site can be well localized by such methods as epididymal aspiration and the injection of dye or radiopaque material into the vas deferens, vasotomy may be tried. This procedure has been reported successful in a sufficient number of patients to warrant encouragement. Hagner[4] has reported cures in twenty-six of eighty-five patients in whom epididymovasotomy was performed.

In the correction of deficient spermatogenesis there is no treatment which is worthy of much praise.

If cryptorchidism is present it should be corrected before the age of 11 years if possible. A single testis, however, is usually adequate for fertility if other factors are normal, and repair of cryptorchidism has not been shown to repair the tendency toward either oligospermia or neoplasm in these glands in the human. We have seen marked diminution of spermatogenic cells in the testes of a boy cryptorchid until the age of 16 years.

Our experience has shown that some patients previously judged to have adiposogenital dystrophy and treated with chorionic gonadotrophin may later have relatively severe oligospermia in spite of the fact that gross evidences of the previous diagnosis have disappeared. This suggests the possibility of some fault in testicular development.

Varicocele and hydrocele if unrepaired may lead to damage of spermatogenesis, but it is unlikely that much improvement can be expected when severe damage to spermatogenesis has occurred. Local infections should be treated by the urologist by appropriate means with or without the aid of the sulfonamides or penicillin or other antibiotics. General infections if present may be important, and obviously such metabolic or endocrine disorders as may be associated with pituitary disease or diabetes require appropriate care. Malnutrition, if associated with underweight, should be treated by a diet of sufficiently high caloric content to bring the weight to normal, and obesity if present should be corrected. It is not unlikely that excessive obesity in some cases may be intimately associated with faulty spermatogenesis.

Though high temperatures and vitamin deficiencies, especially of vitamin E, have been abundantly shown to have serious deleterious effects in animals, there is almost no information to indicate that such factors are important in the human. I have personal knowledge of five men whose wives have had children or are pregnant since the husbands returned from army service. These men were subjected to severe malnutrition and vitamin deficiencies for nearly two years in a Japanese prison camp. In spite of such information, when the nutritional history is poor and metabolic demands have been great, and when the oligospermia cannot be adequately explained it is probably good practice at the present time to be certain that the patient receives more than the adequate amount of vitamins A, B and E.

The use of thyroid is generally considered worthy of a trial if the metabolic rate is low and the low rate of probable thyroid origin. Anxiety and fatigue should be eliminated, and a healthy, well balanced regimen of living arranged.

Sex Hormone Therapy.—Sex hormone therapy for sterility in men has fallen far below original expectations. This is due partly to the fact that diagnosis is usually inadequate, and treatment is tried when no endocrine cause for the abnormality has been demonstrated.

This is not the only reason, however; probably a more important one is the fact that the disorder in many instances is irreversible. Testicular biopsies are of great assistance in the proper selection of such patients for treatment.

Sex hormones to be considered in therapy are: (1) pituitary gonadotrophin (pituitary gland extract), (2) equine gonadotrophin (pregnant mare's serum extract), and (3) chorionic gonadotrophin (human pregnancy urine extract).

The extreme paucity of good reports on production or maintenance of spermatogenesis with any of the above preparations makes it apparent at once that their over-all clinical value is limited. Occasional good reports on some of them, however, appear to be bona fide. At the present time any evidence of improvement ascribed to treatment must be viewed critically. Increases in sperm count may be due to a change in general health, such as recovery from infection. The occurrence of pregnancy during treatment with gonadotrophins may not be associated with an adequate shift in sperm production to warrant the conclusion that treatment was the cause of conception. The most convincing responses are those in which repeated semen examinations show consistent and sustained rises in sperm population to a level approaching normal, especially if a subsequent fall follows withdrawal of treatment.

Theoretically, the most promising of these substances is pituitary gonadotrophin. If the preparation is made from horse pituitary extract the possibility of allergic responses should be checked by appropriate tests before treatment is begun. It may be used in doses of 100 to 500 international units daily or on alternate days. It should be kept in mind that the good effects of treatment if continuous may be impaired by the formation of antihormones. Rowlands[5] demonstrated the development of antigonadotrophic hormones in the sera of patients treated with pregnant mare's serum extract. Others have failed to show such an effect; for example, Saphir[6] and Fellows[7] failed to detect antigonadotrophic effects in the sera of humans treated with pregnancy urine extract.

This material may be given alternately with the chorionic gonadotrophin 500 to 1000 I.U. so that each is received on alternate days or each is given daily in alternate weeks.

Equine gonadotrophin (pregnant mare's serum extract) in doses of 1 cc. per day may be tried. This material should be tested for allergic properties before it is given. It is probably unwise to use it continuously for more than three weeks at a time without a rest period of one to two weeks, during which time chorionic gonadotrophin may be used if desired. Recently it has been our practice to employ pituitary or equine gonadotrophin only when testicular biopsy demonstrates sufficient functional spermatogenic tissue to make a good result appear within reasonable hope. Courses of three weeks are usually used, each

course ending at a time calculated to be just past a normal ovulation date. Testosterone has found no place in the treatment of infertility in spite of the fact that it is capable of maintaining spermatogenesis in hypophysectomized animals.[8] Large doses are known to depress sperm counts,[9, 10] but it is doubtful whether or not this occurs with such doses as are usually employed.[5] Pregneninolone has been suggested for use by Masson,[11] but its place in clinical practice has not been established.

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EVALUATION OF ADRENAL CORTICAL FUNCTION IN MAN

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THE extensive experimental studies of the last fifteen years have revealed the important role the adrenal cortex plays in many physiological processes. The application of this knowledge to clinical medicine has been somewhat delayed owing in part to the lack of satisfactory methods for the evaluation of adrenal function. Until very recently the manifestations of disorders in adrenal function could only be ascertained by the association of metabolic disturbances with gross pathological changes in the gland observed at operation or at postmortem examination. It was by this method that the relationship of Addison's disease and the adrenogenital syndrome to conditions causing hypofunction and hyperfunction, respectively, of the adrenal gland was established. In many patients, however, all the features of a particular syndrome known to be associated with abnormality of adrenal function may not be present and in them it is usually only by inference that malfunction of this gland can be considered to account for the clinical findings. Also different adrenal functions may be disturbed quite independently of one another and clinical evaluation does not always allow one to determine which one is at fault, nor does it permit a quantitative measurement of the disorder.

Various aspects of metabolism as well as the diagnosis and treatment of disorders of the adrenal gland have been reviewed in these clinics and methods of evaluating adrenal function have also been discussed. It is chiefly the purpose of this paper to consider some of the methods that have been developed recently for the measurement of adrenal cortical substances and to discuss their application to clinical medicine. Other methods of evaluating adrenal function, which have been previously discussed in these clinics, will be referred to only briefly.

FUNCTIONS OF THE ADRENAL CORTEX

A great variety of functions have been attributed to the adrenal cortex. For clinical purposes it is useful to classify them into three major groups: (1) regulation of water and electrolyte metabolism; (2) regulation of carbohydrate and protein metabolism; (3) production of sex hormones.

Evidence has accumulated in recent years to show that these functions of the adrenal gland can be associated with different types of adrenal hormones elaborated by the cortex. The isolation of numerous compounds from extracts of the adrenal gland has established that the

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active hormones of this gland are steroids. At least twenty-eight such chemically pure and characterized steroids have been isolated. Not all of these have so far been shown to possess biological activity. At least six of these hormones are capable of maintaining the life of the adrenalectomized animal. Undoubtedly there exist still other potent hormones in the cortex which have not been isolated, since the amorphous fraction which remains after the removal of numerous crystalline hormones still possesses marked activity in maintaining the adrenalectomized laboratory animal. These steroid hormones can be classified according to their biological activity into three groups which correspond to the three main functions of the adrenal gland as already outlined.

1. Compounds which affect water and electrolyte metabolism, such as desoxycorticosterone and the "amorphous fraction."
2. Compounds which affect carbohydrate and protein metabolism. These are corticosterone, dehydrocorticosterone and their two 17-hydroxy derivatives.
3. Steroids with the properties of the sex hormones. In this group fall the androgens, the estrogens and progesterone.

METHODS FOR EVALUATING ADRENAL FUNCTION

There are a number of laboratory procedures which may be used as aids in the diagnosis of states of hypo- and hyperfunction of the adrenal cortex. Some of these consist of measurements in blood or urine of the compounds secreted by the adrenal cortex or of their metabolic products, while others include the use of various metabolic indications such as disturbances of electrolyte and carbohydrate metabolism which have been shown to be influenced by adrenal cortical function. An outline of the various tests which have been used for determining adrenal function are listed in Table 1.

Electrolyte and Water Metabolism.—In both experimental animals and man, adrenal insufficiency is characterized by a failure of the kidney to retain sodium chloride and to remove potassium from the body. Consequent upon these inabilities to regulate electrolyte metabolism are corresponding changes in extracellular fluids. Some of the methods in use for evaluation of this particular function are the determination of the concentration of sodium, potassium and chloride in the serum. These estimations are of only limited value in the evaluation of adrenal function, for it is only in the acute phases of adrenal insufficiency that there is likely to be a decrease in the concentration of sodium and chloride and an increase in the level of potassium, and other conditions such as dehydration and salt loss, which occur in vomiting, may result in these changes. It might be expected that in conditions of overfunction of the adrenal cortex the electrolyte changes in the blood would be the opposite to those observed in states of adrenal underfunction. Only rarely, however, is this observed. This is

probably due to the fact that not all conditions of hyperfunction of the adrenal cortex result in an excessive secretion of those hormones which regulate electrolyte metabolism.

The water diuresis test proposed by Robinson and associates of the Mayo Clinic has been extensively applied as a means of determining the presence or absence of adrenal insufficiency in patients in whom Addison's disease was suspected. Additional information can be ob-

TABLE 1

OUTLINE OF TESTS FOR DETERMINING ADRENAL FUNCTION

	Hypofunction (Addison's Disease)	Hyperfunction	
		Adrenogenital Syndrome	Cushing's Syndrome
I. Electrolyte and Water Metabolism	Concentration of serum sodium, potassium and chloride Water test Water test combined with urea and chloride clearance Chloride excretion during period of salt restriction		Concentration of serum chloride and bicarbonate.
II. Carbohydrate Metabolism	Glucose tolerance test Insulin sensitivity test Excretion of glycogenic corticoids	Excretion of glycogenic corticoids	Glucose tolerance test Insulin sensitivity test Excretion of glycogenic corticoids
III. Production of Sex Hormones	Excretion of 17-ketosteroids	Excretion of 17-ketosteroids Ratio of α to β 17-ketosteroids Excretion of estrogens Excretion of pregnandiol	Excretion of 17-ketosteroids

tained with regard to electrolyte balances if the procedure of Robinson, Power and Kepler[1] is carried out during the water test. Cutler, Power and Wilder[2] have suggested another test for the detection of hypofunction of the adrenal which is based upon the fact that patients with Addison's disease continue to lose salt in the urine even when the intake of sodium chloride is restricted. At present there are no methods available for detecting in blood or urine those hormones which directly affect electrolyte and water metabolism.

Carbohydrate and Protein Metabolism.—Extensive research on experimental animals has revealed that the adrenal cortex has also a direct influence on carbohydrate and protein metabolism. Administration of adrenal cortical hormones to adrenalectomized animals results in an increase in blood sugar and liver glycogen. This is partly due to an increased catabolism of protein and also to an inhibitory effect of the adrenal steroids on the oxidation of glucose in the peripheral tissue. The amino acids derived from the breakdown of tissue proteins yield residues which after deamination may form glucose or be utilized in some other way.

The adrenal cortical compounds that have been associated with the regulation of carbohydrate and protein metabolism are the group of substances known as the "corticosterones." They all possess an oxygen atom on C_{11} and have the ability to cause gluconeogenesis. It has been shown in man that there are substances excreted in the urine which have the same biological activity as the corticosterones, i.e., they are capable of prolonging the life of adrenalectomized animals and will cause an increase in liver glycogen when administered to fasting adrenalectomized animals. Recently the measurement of these urinary metabolites has been used as an index of the activity of the adrenal in regulating carbohydrate metabolism. Several methods have been proposed for the assay of these hormones,[3, 4, 5, 6] and all are based upon the effect that these substances have upon the deposition of glycogen in the livers of adrenalectomized animals.

As in the case of all studies of excretion products of hormones, there are numerous factors which affect the level of excretion other than the actual amount of active substances in the gland. The quantity of active substances found in the urine is relatively small and probably in no way indicates absolute amounts of corticoids elaborated by the gland itself, but large numbers of assays carried out in our laboratory, and by others, suggest that the variation in excretion of these active substances reflect the activity of the adrenal gland. This bioassay measures only those compounds which possess the property of affecting carbohydrate metabolism and will not detect changes in adrenal function affecting compounds having androgenic activity which do not possess this property. Using this method as a means of evaluating carbohydrate function, Venning and Browne[7, 8] have reported findings on a series of cases with endocrine disorders. These will be discussed in detail later.

Colorimetric procedures based upon the reducing properties of adrenal steroids have been developed by Talbot and co-workers[9] and by Heard and Sobel.[10] These chemical methods may include metabolites of adrenal hormones which are not active in the biological test and all give higher values. A correlation of their results with clinical findings suggests that these chemical procedures are measuring the ex-

cretion of adrenal compounds concerned with the regulation of carbohydrate function.

The glucose tolerance test and the insulin sensitivity test have been used extensively as an index of hypo- or hyperfunction of the adrenal. These are indirect measurements which may be affected by other glands and other factors. Hypoglycemia and increased glucose tolerance is frequently associated with Addison's disease, although normal adrenal carbohydrate function can exist at the same time with disturbed electrolyte and water metabolism. In hyperfunction of the adrenal, two distinct types are recognized. They are the adrenogenital syndrome and Cushing's syndrome. In the former the hyperplastic adrenal cortex or the adrenal tumor is producing excessive amounts of those sex hormones which are androgenic in action. Accordingly, the changes observed are those of virilization. In Cushing's syndrome, on the other hand, many of the manifestations of the disease appear to be the result of over production of those hormones which regulate carbohydrate and protein metabolism. In this syndrome the glucose tolerance is impaired and insulin resistance is found.

Androgenic Function of Adrenal, 17-Ketosteroids and Androgens.—The term 17-ketosteroid was originally applied by Callow, Callow and Emmens (1936) to a group of steroids found in urine which have a ketonic group at the seventeenth carbon atom and a free methylene group. These steroids give a characteristic pink color with alkaline dinitrobenzene, a reaction described by Zimmerman in 1935. Many modifications of the Zimmerman reaction are in use in various laboratories for the assay of these compounds. Recently a new color reaction which is specific for certain of the 17-ketosteroids has been developed by Pincus (1943).

Some of the 17-ketosteroids have androgenic properties and biological methods have been used for determining the androgenic potency of urinary steroids. Because the colorimetric tests measure both active and inactive compounds, results obtained by the former are always greater than those obtained by the bioassay.

Most of the clinical observations suggest that the adrenals are the principal source of the urinary 17-ketosteroids and the androgens. In the male, part are also derived from the testes. Fraser and co-workers[4] concluded that two-thirds of the 17-ketosteroids in male urine are of adrenal origin and one-third are from the testis, while those present in female urine are considered to be metabolites of only adrenal hormones.

The adrenal precursors of these substances have not as yet been identified, but it is generally believed that they are concerned with the androgenic function of the adrenal and have an anabolic effect on protein metabolism. In hypofunction of the adrenal gland due to Addison's disease there is a decrease in excretion of 17-ketosteroids. Similarly low values are found in cases of panhypopituitarism.

In cases of simple hirsutism, the 17-ketosteroid excretion may be normal or slightly increased, whereas in patients with adrenal cortical hyperplasia or adrenal cortical carcinoma an abnormally high excretion of 17-ketosteroids is usually found.

Talbot and co-workers[6] have suggested that the differentiation of 17-ketosteroids into α and β fractions may be of diagnostic value. They found that the β-17-ketosteroids were elevated in patients with adrenal cortical carcinoma whereas in cortical hyperplasia this fraction was either normal or slightly elevated. Dobriner and co-workers, using chromatographic methods of fractionation of urinary steroids, find that not only the amount but also the type of 17-ketosteroid excretion is of significance in certain disorders.

STUDIES ON THE EXCRETION OF GLYCOGENIC CORTICOIDS AND 17-KETOSTEROIDS IN ENDOCRINE DISORDERS

A study of the excretion of glycogenic corticoids and 17-ketosteroids in a series of normal individuals and in various endocrine disturbances has been carried out in our clinic. The results are shown in Figure 27.

With a measurement of these two groups of metabolites of adrenal hormones, the activity of two different aspects of adrenal function in the same individual can be determined. The amounts of glycogenic corticoids excreted per day are of a much smaller order than the 17-ketosteroids. An average of 60 microgram equivalents of 17-OH-11 dehydrocorticosterone is excreted per day by normal men, whereas normal women excrete approximately one-third less. Similar variations in the daily output of the corticoids and 17-ketosteroids were seen but the fluctuations in the excretion of these two types of adrenal metabolites did not necessarily parallel one another. Little or no corticoids are found in the urine of the newborn child, although large amounts of these active substances are excreted by the pregnant woman in the last trimester of pregnancy. In the growing child, the maximum level of excretion of corticoids is attained around seven years. On the other hand, the 17-ketosteroid excretion increases at a slower rate, only reaching adult levels at puberty.

Among the various cases of disturbances of adrenal function which have been studied, the majority of patients with Addison's disease showed a marked decrease in the output of both 17-ketosteroids and urinary corticoids. In a few instances, however, a normal output of corticoids was found associated with a decreased output of 17-ketosteroids, thus suggesting the possibility of having hypofunction of one aspect of adrenal metabolism without affecting the other functions.

In cases of panhypopituitarism a marked lowering of the excretion of both adrenal metabolites is found. In several cases of anorexia nervosa where the hypofunction of the adrenal gland has been regarded as occurring as a consequence of the malnutrition, the 17-

ketosteroids and corticoids were lowered but not as low as those found in cases of panhypopituitarism.

In several cases of simple hirsutism where no other signs of virilism were present, the glycogenic corticoids were normal, while the 17-ketosteroids were increased. In all the cases of active Cushing's syndrome investigated the values for glycogenic corticoids were markedly

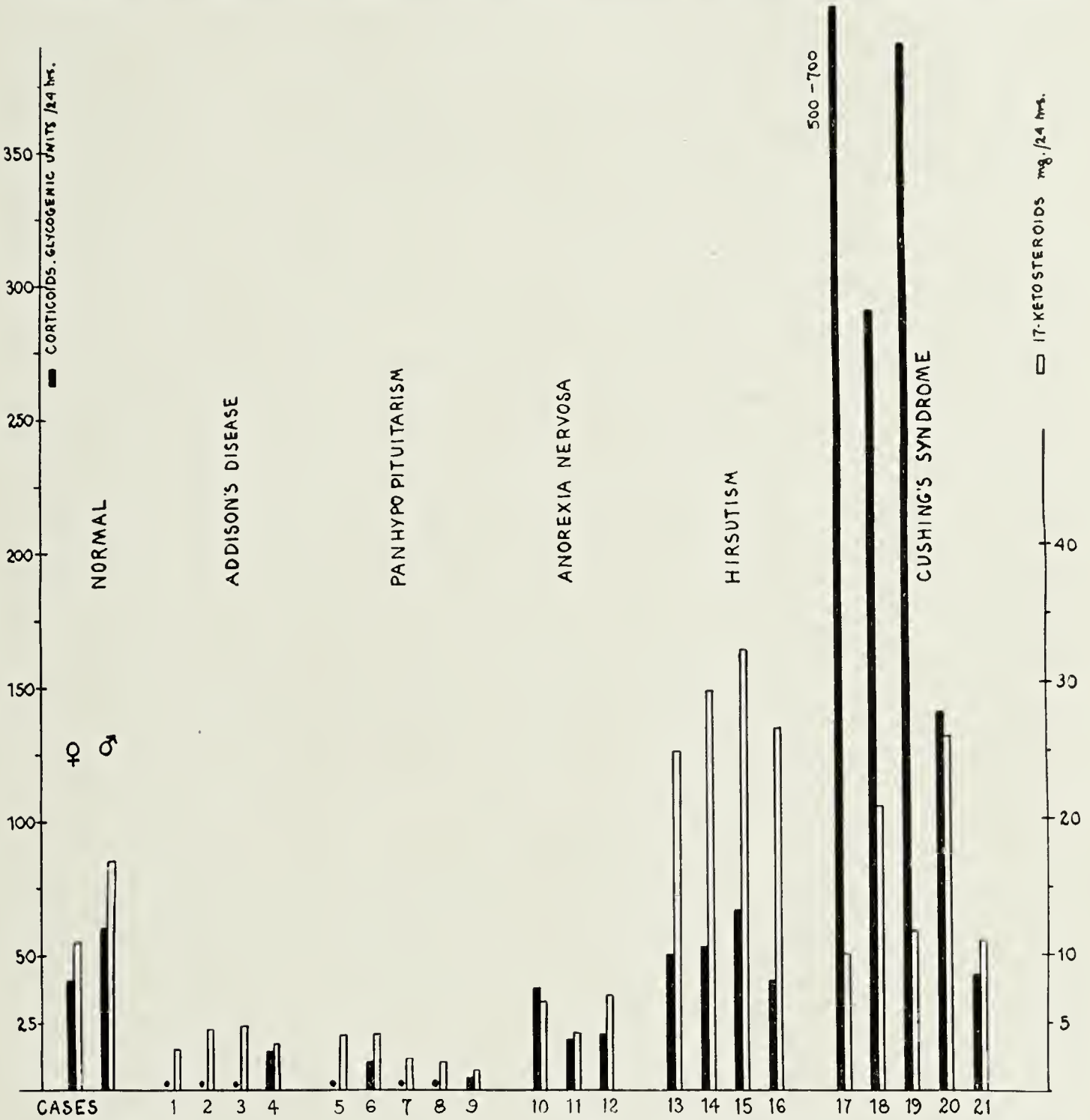

Fig. 27.—Excretion of glycogenic corticoids and 17-ketosteroids in normal individuals and in patients with adrenal disturbances. (J. Clin. Endocrinol., 7:79, 1947).

increased, while the 17-ketosteroids were either normal or only slightly elevated. In these cases the degree of impairment of the glucose tolerance curve did not always parallel the increase in corticoid excretion. In cases of adrenal hyperplasia and tumor reported by Dobriner, both the 17-ketosteroids and corticoids were increased.

The results of these studies indicate that it is possible that the three main types of adrenal cortical function may vary independently of one

another, so that the clinical signs and symptoms produced and the metabolic findings may vary, thus leading to a variety of syndromes all associated with hyper- or hypofunction of the adrenal cortex.

Other Factors Influencing the Output of These Substances.—The experiments of Selye and others have shown that one of the earliest responses of the organism to toxic agents or trauma is hypertrophy of the adrenals. This can be observed in man by following the excretion of the adrenal metabolites. Following trauma, such as fractures, burns, surgical operations or infections, there is an immediate rise in the excretion of the glycogenic corticoids. This increased excretion of adrenal metabolites is maintained from five to fifteen days depending somewhat upon the severity of the damage and then returns to normal levels. A temporary rise in 17-ketosteroid excretion is frequently observed. Strenuous muscular exercise will also cause a marked increase in output of the corticoids.

Excretion of Pregnandiol and Estrogens.—The presence of pregnandiol in the urine of virilized women in whom the ovarian function is completely suppressed, is an indication of hyperfunction of the adrenals. This substance has been shown to be a metabolite of progesterone and desoxycorticosterone and both these compounds have been isolated from the adrenal cortex. Considerable amounts of this substance have been found in the urine of patients with adrenal hyperplasia or adrenal tumors of the virilizing type. Several cases have been reported in which adrenal tumors were associated with increased excretions of estrogens. This is not a consistent finding; however, the presence of large amounts of estrogen and the lack of gonadotropins may be of diagnostic value in evaluating adrenal function.

SUMMARY

The methods in use for the evaluation of adrenal function have been reviewed with special emphasis on the measurement of urinary glycogenic corticoids as a means of determining disturbances in the carbohydrate function of the adrenal.

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THE PHYSIOLOGICAL BASIS OF HYPOGONADISM IN THE MALE

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THE term hypogonadism by common definition and usage has come to be regarded as relating only to a state of reduced endocrine activity of the gonads and it is customary to envision an individual of eunuchoidal physical proportions and retarded sexual development as typifying the hypogonadal state. The coexistence of hypogonadism and eunuchoidism is, of course, not uncommon, but the latter is by no means a constant concomitant of the hypogonadal state. In males it is only those individuals whose testicular failure occurs prior to or early in the pubertal period who show the various stigmata of the eunuchoidal state—underdeveloped genitalia, high-pitched voice, scarcity of facial and body hair and eunuchoidal physical proportions. Furthermore, eunuchoidism occurs only in those men whose testicular failure includes or is confined to its endocrine activity. Thus it is essential at the outset of any discussion of our present knowledge of hypogonadism to call attention to the fact that underfunction of the testis may involve impairment of the production of germ cells only, decreased secretion of testicular hormone only, or a combination of the two. If the gametogenic function only is involved the sole manifestation of the hypogonadal state is impaired fertility.

It is important therefore to realize that the hypogonadal state actually may be divided into a number of rather distinct categories.[1] These depend on the age at which the testicular defect occurs and on the testicular function which is impaired. A correct classification should also take into account whether or not the failure is primary to the testes or is due to inadequate stimulation of the testes by the hypophysial gonadotrophic hormones, i.e., secondary testicular failure. Most students of the problem now agree that the anterior lobe of the hypophysis secretes two hormones which are intimately concerned with testicular function. The so-called follicle-stimulating hormone (FSH) stimulates the maturation of germ cells in the seminiferous tubules while the interstitial cell-stimulating hormone (ICSH) is necessary for the proper function of the interstitial cells of Leydig in the production of androgenic hormone. Failure of the hypophysis to secrete adequate amounts of either or both of these factors is reflected in impairment of the respective target tissues.

Certain laboratory procedures are of primary importance in prop-

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erly diagnosing the various types of hypogonadism. Gross examination of the testes and sex accessory organs and characters, study of semen samples and examination of the patient's physical proportions and characteristics are useful, of course, and should be made in each instance. However, these measures frequently reveal little or nothing as to the precise nature of the gonadal defect nor do they offer an entirely secure basis for proper therapeutic procedures. We have found that the combination of *testicular biopsy* and *assay of urinary gonadotrophins* usually provides the additional information which is needed for complete diagnosis. The urinary gonadotrophins alone will serve in most instances to differentiate between primary and secondary failure of the testis. Patients whose pituitaries are producing inadequate quantities of the gonadotrophic factors show low titers of urinary gonadotrophin while men whose hypogonadism is due to primary failure of the testes have high levels of urinary gonadotrophin. On the basis of this assay it is usually possible to predict whether treatment with gonadotrophin has even a reasonable chance for success or whether treatment with androgenic hormone provides the only means of correcting the physical stigmata of hypogonadism. Experience has shown that men whose levels of urinary gonadotrophin are high rarely respond to treatment with such preparations of gonadotrophin as are available. This is not surprising since they do not respond to their own hypophysial hormones.[2, 3]

Of even greater diagnostic value is the testicular biopsy. This relatively simple procedure[1, 4, 5, 6] reveals the precise character of the deficiency and its dependability urges its use as a routine procedure in all instances of hypogonadism in which surgical procedures for relief of obstructed efferent ducts or therapy with gonadotrophins are under consideration. Useful information from the standpoint of the endocrine function of the testes is achieved through a study of the urinary levels of 17-ketosteroids and estrogens, but their value from a diagnostic or clinical standpoint is not commensurate with the technical difficulties. Furthermore, the participation of the adrenal cortex in the production of 17-ketosteroids and estrogens must always be considered. The combination of testicular biopsy and assay for urinary gonadotrophin together with physical examination furnishes adequate information for diagnosis and treatment. In instances of low sperm count the biopsy will reveal whether or not the germinal epithelium is producing sperm or is capable of responding to treatment with gonadotrophins. Such information provides an intelligent and accurate basis for considering or dismissing operative procedures or therapy with gonadotrophins, as the case may be.

As noted earlier in this discussion hypogonadism may be classified in two principal groups, viz., gonadal deficiency stemming from defects of the testes and testicular failure due to inadequate secretion of hypophysial gonadotrophins. Various subdivisions of these may be

recognized on the bases of the nature of the defect, the testicular component which is involved, and the age at which the defect appeared.

I. PRIMARY FAILURE OF THE TESTES

In cases of this type the hypophysis, with rare exceptions, is producing at least normal amounts of gonadotrophin, but for one reason or another the testes fail to function normally. The defect may be in either or both testicular components and may occur prior to puberty, during the pubertal years, or at any age thereafter. The time at which failure occurs determines to a considerable extent the effect upon the individual.

A. **Failure of the Testes Prior to or Early in Puberty.**—1. *Failure Involving the Gametogenic and Endocrine Functions of the Testes.*—In cases of this group the testes are either absent or if present are small and usually soft. Included under this heading are instances of congenital absence of the testes and of traumatic atrophy.[2] Cases of the latter type are seen most commonly as a sequel of faulty surgery for conditions of cryptorchidism. Inflammatory disease of the testis may so seriously damage the organ that recovery does not occur and both sterility and deficiencies of androgenic hormone are apparent later if the destructive lesions are bilateral. However, inflammatory diseases are apparently not as likely to cause permanent damage to the prepubertal testis as they are to the gonads of older individuals. Malignant disease of the testes may occur in young boys, but it is more commonly seen during later life. We have seen a few instances of gonadal failure which seemed to be explained best on the basis of a constitutional defect of the gonadal tissue. In such instances the gonadotrophin levels are low or normal and the testes fail to respond to treatment with gonadotrophins although biopsies reveal that a response may be expected. Indeed, the testicular tissue resembles that seen in cases wherein the testes fail to mature because of inadequate stimulation by gonadotrophic hormone. The so-called Klinefelter syndrome which is also believed to arise as a result of constitutionally defective gonadal tissue may also make its appearance at the onset of puberty. This syndrome is considered in more detail under B,1, since it appears to become manifest more commonly at a somewhat older age.

2. *Failure of the Gametogenic Function Only.*—Some of the etiologic factors which are responsible for complete prepubertal failure of the testes may operate to impair gametogenic function only. Failure of testicular descent, inflammatory disease and defective germ cells are each responsible for instances of impairment of the spermatogenic activity of the testes. For a time, at least, in such cases this function only may be affected.

3. *Failure of Endocrine Function Only.*—Theoretically one might expect to observe instances of failure of the mesodermal elements, which normally differentiate into Leydig cells and produce androgen

when properly stimulated by ICSH, to occur independently of failure of gametogenic function. However, I have not encountered such cases nor am I aware of reports of such a condition. There is a very strong possibility that the condition does not exist since there is considerable evidence which indicates that androgenic hormone may play an important role in the normal function of the seminiferous tubules.[8] If such proves to be true it is likely that normal spermatogenesis would not occur in the absence of proper function of the Leydig cells.

B. **Failure of the Testes During Puberty or the Early Postpubertal Years.**—1. *Failure of Both Endocrine and Gametogenic Functions.*—Testicular failure during puberty or the early postpubertal years arises from much the same factors as described for earlier failure, with the exception of congenital absence of the testes. In size the testes may be somewhat larger than in cases of prepubertal failure, but they rarely approach the normal in size or consistency. As far as the condition in the testes themselves is concerned, the chief difference is some evidence that testicular function had undergone at least a transitory period of activity. The presence of differentiated germ cells, seminiferous tubules which are larger, and evidence of some degree of activity in the Leydig cells, all are indicators of the fact that the testes have had a period of more or less normal function. These conditions may not be strikingly evident particularly if the biopsy is not obtained, as is frequently the case, for some years after the onset of failure. In such instances the best clue to the age at which the defect made its appearance lies in the physical characters of the individual.

When failure of the Leydig cells does not occur until puberty is underway or completed the patient shows development of physical proportions and secondary sex characters commensurate with such physiological age. It is, of course, true that evidence of deficiency of androgenic hormone may be present in such individuals, but the picture is never that seen in those cases in which failure occurs before puberty. Gynecomastia, too, is seen in many of these individuals while it is usually not present in instances of prepubertal failure.[3] In either case sterility is an inevitable and usually irreversible consequence. If failure does not occur until spermatogenesis is well established some tubules may continue a form of spermatogenesis for a considerable length of time although the germinal epithelium is disorganized and many of the spermatozoa which are formed are abnormal. Aside from those causes of failure which are prone to cause rapid involution of testicular tissues, such as inflammatory disease, faulty surgery or traumatic damage, the principal factor involved in cases of testicular failure which occur during or shortly after puberty appears to be a constitutional defect.[9] The latter type of failure was first described by Klinefelter, Reifenstein and Albright[10] and studied further by Heller and Nelson.[3, 9, 11]

Primary testicular failure occurring after the onset of the striking

changes which take place at puberty may be properly regarded as a destructive lesion whether the cause is inflammatory disease, trauma or constitutional defectiveness, since the constant picture is one of widespread involution of the testicular components. In every instance which has come to our attention before the destructive changes have caused complete atrophy of the tubules and Leydig cells the seminiferous tubules appear to have been affected first while the Leydig cells present a variable picture. They may show relatively little change from the normal, particularly if the testis is examined soon after the atrophic condition is presumed to have had its onset, or they may present a picture of widespread involution to more primitive types of connective tissue elements. Perhaps the vascular changes which accompany or follow atrophy of the seminiferous tubules have a deleterious effect upon the Leydig cells. In any event more often than not the intertubular cell population shows a marked decline in the number of elements which by cytologic criteria[9, 12] are regarded as functional Leydig cells. In cases of this group in which serial biopsies have been procured, the later samples have shown progressive involution of the Leydig elements.

2. *Failure of the Gametogenic Function Only.*—As noted above, it is spermatogenesis which usually suffers earliest and most acutely in primary testicular failure arising after the onset of puberty. Indeed, in some instances in which the testes are examined early enough one cannot be certain that involutionary changes have extended to the Leydig cells to a significant degree. Perhaps the case of the undescended testicle is very much to the point in this regard. Although it is commonly believed that this condition does not interfere with function of the Leydig cells there is a considerable body of evidence which indicates that the production of androgenic hormone is reduced particularly in instances where both testes have remained undescended for long periods of time.[8, 13, 14] Nevertheless it is reasonable to classify the hypogonadism which arises from failure of the testes to descend into the scrotum under the present heading since such gonads are probably morphologically normal until puberty. At that time the seminiferous tubules are unable to respond to the rising level of gonadotrophin although the Leydig cells are stimulated to produce androgen.

In undescended testicles obtained during or soon after the pubertal period the Leydig cells appear to be cytologically normal. However, in other instances in which the testes were studied ten or twenty years after puberty the number and cytological appearance of the Leydig cells have been regarded as indicating lessened production of androgen. In other instances of primary failure of gametogenic activity, due to inflammatory disease, the Leydig cells may remain morphologically normal and the individuals present no evidence of androgenic insufficiency. Indeed, the extent of tubular damage may be quite variable in accordance with the number of tubules which were damaged and

the regenerative capacity of the germinal epithelium. The capacity for repair varies considerably from tubule to tubule as has been shown in the case of testes returned to the scrotum after having been anchored in the abdominal cavity.[15]

3. *Failure of Endocrine Function Only.*—The remarks which were made under A, 3, are equally applicable here. Although it is entirely possible that this condition may occur, we have not seen an instance of Leydig cell impairment in the presence of normal gametogenic activity.

C. **Failure of the Testes After the Second Decade of Life.**—Although instances of failure of both testicular components occur in this age group there appears to be less tendency for such to be true than in younger males. There are two reasonably clear-cut categories representing the two testicular components separately. Such overlap as has been observed will be considered under the respective headings.

1. *Failure of Gametogenic Function.*—Included here are most of the cases of infertility which come to the attention of the general practitioner or the specialist. The usual picture is of a childless man in the age range of 25 to 40 years who is masculine enough in all respects and whose wife apparently is fertile. In contrast to the men of the groups discussed under A and B the testes of such an individual are usually fairly normal in size and consistency. Examination of his semen has revealed aspermia, azoospermia, high percentages of abnormal sperm or some degree of oligospermia, and assay of his urine for gonadotrophin has shown a normal level. Testicular biopsy in such an individual reveals one of two conditions:

(*a*) Reasonably normal spermatogenesis, in which case the cause of the sterility is not the testes, but is a defect (obstruction or congenital absence) of the efferent duct system. There is the chance in such cases that surgical intervention will establish proper exit for the spermatozoa which the testes are producing.[7]

(*b*) A picture of disturbed spermatogenesis. In this instance the type of disturbance and its extent determines to a considerable extent the treatment and prognosis which apply to the case in question. The most common condition which one encounters involves widespread disorganization of the germinal epithelium, sloughing of immature germ cells and peritubular fibrosis. The latter is a constant concomitant of damage in any form to the germinal epithelium although the type and degree of fibrosis, number of tubules involved and rapidity of progression may vary considerably. Not infrequently one observes aberrations of cell division or chromosomal behavior in the germ cells. These include failure of the daughter nuclei of the first maturation division, i.e., primary to secondary spermatocytes, to occupy separate cells.

The same phenomenon may occur in the second maturation division in which the secondary spermatocytes divide to form spermatids. Incomplete partitioning of chromosomal material may take place at either

division. The result is cells with two nuclei or cells with large or small nuclei. The consequence of such behavior is seen in the resulting spermatozoa which show various types of abnormality, duplicate, giant and dwarf forms. Such abnormal mature cells can be found in the tubules and, of course, in the semen specimen. The extent of such abnormalities determines to a considerable degree the prognosis of the case particularly if the defect is accompanied, as it sometimes is, by a demonstrable obstruction in the system of efferent ducts.

Of gravest concern in these cases which show disorganization of the germinal epithelium is the extent to which activity of the spermatogonia is affected. If these are numerous and show evidence of good mitotic activity the testis can be regarded as having retained the capacity to form new cells in sufficient quantities to carry on the spermatogenic process. However, in many instances they are reduced in numbers and show infrequent mitoses, evidence that the regenerative capacity of the germinal epithelium is seriously impaired. In such cases peritubular fibrosis is usually very evident and the combination of disorganized germinal epithelium, impaired activity of spermatogonia and moderate to severe peritubular fibrosis affecting 50 per cent or more of the tubules is regarded as evidence of hopelessly impaired fertility. Probably the outlook, under our present understanding of the causes of the defect and means of treatment, is hopeless when the percentage of tubules so affected is even less and we regard 50 per cent as an optimistically conservative estimate. However, many more cases must be studied before our understanding of the factors involved is on a sufficiently secure basis to warrant closer calculation.

Since cases of this type present a common problem in male infertility it is important that we gain some understanding of the basic causes at work if treatment is to be carried out intelligently and effectively. Unfortunately we are not in a position to offer an explanation which embraces all or even a large percentage of the cases in this group. Others[6, 7, 16, 17] who have observed the condition either have been unable to offer a satisfactory explanation or have made no attempt to do so. Our own observations, covering approximately 120 cases of this type, have led us to believe that the same condition may arise from a variety of causes. Arteriosclerotic changes in the testicular vessels may account for a small percentage of those seen. Episodes of generalized nutritional deficiency or inflammatory disease which at some earlier time initiated unrecognized, but progressive, damage to the testis are likely factors.

Since the close of the war we have seen a large number of sterility cases in young men who present a history of inadequate nutrition and episodes of tropical disease accompanied by varying types of treatment. As yet we know too little of the manner in which these factors affect the human testis, but it is not unlikely that a tissue as labile as the seminiferous epithelium appears to be may suffer unrecognized

damage which progresses after the primary cause long since has been eradicated. In these as well as other cases which do not present histories of such suspect character we must again recognize the possible participation of a constitutional defect of the germinal cells which leads either to their early spontaneous decline or renders them unusually susceptible to deleterious influences from which they do not easily recover. The same influence, i.e., nutritional disturbances or inflammatory disease, in more fortunate individuals may cause merely a temporary derangement of gametogenic activity from which recovery subsequently occurs in at least the majority of tubules.

As noted above, it is unlikely that men in this group are suffering from an endocrine disturbance and therefore we have no reason to believe that therapy with available hormonal preparations would be of any value. It is worth noting that although most of the men in this group have normal urinary levels of gonadotrophin, some of them show elevated levels. It is significant, too, that there is a tendency for the Leydig cells in these cases to show evidence of reduced functional activity. Our methods for the assay of urinary gonadotrophin are such that it is not possible to assess accurately the relative amounts of the two gonadotrophic hormones. Therefore it is difficult to relate the findings of high gonadotrophin and poor Leydig cells. The gonadotrophins may be elevated because of the primary failure of the Leydig cells and their inability to produce sufficient androgen to maintain normal hypophysial activity. Other explanations are also possible, but it is useless to speculate in this regard until more facts are available. It is enough to say that the evidence contraindicates endocrine therapy in this group of sterility cases. An attempt is being made[18] to evaluate the plasma and seminal fluid levels of Vitamins A, C and E in patients of this category. It was observed that while the levels of A and E and the plasma level of C were normal, the C content of seminal fluid was distinctly lower than normal. However, attempts to correct the testicular defect by administering added vitamin C have as yet not yielded encouraging results.

A testicular picture which occurs less frequently is one in which fibrosis is mild or absent, spermatogonial activity is good, and primary spermatocytes are numerous, but the spermatogenic process appears to be blocked at that point. The vast majority of primary spermatocytes fail to undergo maturation divisions and few if any mature sperm are formed. Leydig cells in these individuals have appeared normal and hormone levels are within normal ranges. Again we may be dealing with a constitutional defect of some type although we have not had the opportunity to properly evaluate the effect of therapy with FSH in such cases. It is quite possible that the defect simply involves a higher threshold of stimulation of the germ cells to gonadotrophin.

2. *Failure of Endocrine Function.*—This group is made up of men who show evidence of the male climacteric.[19] The testes in such cases

may show some degree of tubular damage such as that described under C, 1, but such is not uniformly true and when it does occur is regarded as a co-existing rather than a related condition. In most instances the tubules are relatively normal except for a type of peritubular fibrosis which we believe is a part of the aging process. This phenomenon occurs in other organs and is seen constantly and to a greater or lesser degree in the testes of men beyond thirty. It appears to progress much more slowly than the type which is associated with grave damage to the seminiferous epithelium. On the other hand, the Leydig cells of men in this group show a reduction in numbers and size, and a disturbance in normal cytological characteristics.[12] The individuals themselves show evidence of inadequate levels of androgenic hormone and have high levels of gonadotrophins. They derive benefit from treatment with androgenic hormone, but do not respond to gonadotrophic hormone. It should be noted that many men who complain of symptoms which resemble closely those seen in the climacteric are not properly members of this group. This can be shown by study of the urinary gonadotrophins and testes and by therapeutic tests with androgenic hormone.[19] Rather they are to be classified under the heading of psychoneurosis and psychogenic impotence. Treatment in their cases is properly psychotherapeutic not endocrine.

II. SECONDARY FAILURE OF THE TESTES

In this form of hypogonadism the testicular tissues have the capacity to function properly, but fail to do so because of the lack of necessary extragonadal influences. Of primary importance in this regard are the two gonadotrophic hormones of the anterior hypophysis. Adrenal cortical[20] and thyroid[21] hyperfunction and hypofunction have been related to gonadal deficiencies in man, but for the most part such studies as have been made have not been complete and as a consequence it is difficult to assess the part which disorders of the adrenal and thyroid have played in hypogonadism. Only in the case of hyperfunction of the adrenal cortex is the relationship reasonably apparent. In such instances the production of large amounts of steroid hormones perhaps upsets the hypophysial-gonadal interrelations through an inhibition of the production of gonadotrophic hormones. On the other hand, the relationship between the gonadal tissues and the hypophysis is clearly evident and it is possible to recognize cases of hypogonadism which are due to an hypophysial inadequacy of prepubertal or pubertal origin and cases in which hypofunction of the pituitary does not occur until later in life. In either event the urinary levels of gonadotrophin are lower than normal. Such a finding together with characteristic pictures in the testicular biopsies may be regarded as pathognomonic of secondary failure due to hypopituitarism.

A. **Failure of the Testes to Undergo Pubertal Maturation.**—In normal individuals the testes undergo very rapid growth beginning at

about age 11 or 12. The seminiferous tubules enlarge and develop lumina as the process of spermatogenesis is initiated and becomes well established. At the same time Leydig cells are differentiated from mesodermal elements and produce androgenic hormone in increasing amounts. However, if the hypophysis fails to secrete adequate quantities of gonadotrophic hormones the testes remain infantile, and the various events of puberty do not occur or do so in a modified form only. It is in cases of this type that eunuchoidal body proportions and undeveloped sexual characteristics are most frequently observed. In the less commonly seen cases of extensive hypophysial failure (panhypopituitarism), insufficiency of other hormones is manifested by small stature, low metabolic rate and evidence of adrenocortical hypofunction.

In either instance, i.e., panhypopituitarism or hypopituitarism confined to production of gonadotrophic hormones, the condition of the testes is similar. They are small and microscopically show an infantile appearance. However, and in this respect they differ from the usual picture in prepubertal primary failure, they do contain considerable numbers of immature germ cells. An additional point of difference is the absence of peritubular fibrosis or hyalinization in instances of secondary testicular failure, at least in men under twenty-five years of age. In older hypogonads of this type, age changes may be superimposed upon the infantile condition of the testes. The intertubular tissue, too, presents an infantile picture and, as a general rule, true Leydig cells are completely absent. The picture, indeed, is quite similar to that seen in the testes of animals which have been hypophysectomized prior to puberty. Furthermore, it is possible to effect definite stimulation of the testes in either case with gonadotrophic hormones.

Our most successful attempts to stimulate spermatogenic activity in men with this type of hypogonadism have followed the use of preparations containing FSH made from pituitary glands.[22] Some success has been achieved with extracts of pregnant mare serum. However, purer and more potent preparations are required before we shall be in a position to realize fully the possibilities of stimulating satisfactory spermatogenesis in this type of hypogonadism. Preparations of human pregnancy urine (chorionic gonadotrophin) have been of no value in stimulating spermatogenesis in these patients since the active material in such extracts is largely interstitial cell-stimulating hormone. However, chorionic gonadotrophin is very effective in stimulating the interstitial cells, and the testes of patients treated in this manner show well developed Leydig cells which undoubtedly are forming considerable amounts of androgen since the secondary sexual characteristics undergo pubertal changes. The results of treatment in such patients will be considered in detail in a forthcoming paper with Dr. Carl Heller. However, it is of value to point out here that both spermatogenic and endocrine activity can be stimulated by suitable gonado-

trophic agents in patients of this group and that it is very probable that in the future even more striking therapeutic results can be expected.

The reason for hypophysial inadequacy in patients of this group cannot be accounted for in every instance. Most frequently it appears that the secretory cells of the pituitary are not functioning at normal levels. The reason for this state of affairs is quite obscure and cannot properly be discussed here. It is noteworthy that some patients of this type, men in the 20 to 30 year group, who were successfully treated have been able to effect continued improvement when therapy was withdrawn. It would seem that treatment had provided a means of removing some block interposed on the secretory activity of the hypophysis, perhaps in the hypophysial-hypothalamic relationship. In addition, the delayed maturation of the testes which is observed frequently in boys, particularly obese subjects, suggests that the hypophysial-hypothalamic system may be involved to an important extent. Of much rarer occurrence are instances of developmental errors or destructive lesions involving the hypophysis. True Fröhlich's syndrome is an example of this type.

Undoubtedly many pathologic conditions impinge on normal function of the hypophysis and may interfere temporarily or permanently with its function. Important among these are inanition, vitamin deficiencies, such chronic disorders as diabetes mellitus and renal disease, and deranged function of the adrenals or thyroid. Correction of the underlying disorder may be expected to result frequently in establishment of normal hypophysial function and, in turn, maturation of the gonads. The proper approach to this problem in any patient clearly involves a thorough study of the case, correct diagnosis, and finally such therapeutic measures as are indicated. Endocrine therapy, important as it may be in some instances, should not overshadow measures to correct disorders of nutrition and metabolism since the latter may be the primary basis for the hypogonadism.

B. **Failure of the Testes During Adult Life.**—Testes which have apparently been entirely normal may fail during adult life as a result of hypofunction of the hypophysis. The latter may occasionally be idiopathic and even be confined apparently to the gonadotrophic function, but in most instances the hypofunctional state probably stems from causes similar to those discussed under II, A. In addition, hepatic cirrhosis frequently causes testicular hypofunction, probably as a result of failure of the liver to inactivate certain steroids, notably estrogenic hormone. The latter, presumably produced in the adrenal, interferes with the production of gonadotrophic hormones and testicular atrophy ensues. Excessive estrogen may not be the only factor involved in hypofunction of the pituitary in cirrhosis since both malnutrition and thiamine deficiency are present in the condition and have adverse effects on hypophysial function.

As is true in those cases of hypofunction of the hypophysis which appear before puberty, it is of primary importance to determine and, if

possible, to correct the cause of the hypophysial defect. However, it is possible to stimulate the testes of adult men with gonadotrophins. This includes both the spermatogenic and endocrine functions, either or both of which may be disturbed in secondary failure during adult life. The success of treatment is conditioned not only by the preparations which are used, but also by the secondary changes which may have occurred in the testes. Chiefly, this involves the severity of peritubular fibrosis and hyalinization which may be present as an aging process unrelated to the immediate effects of hypophysial hypofunction and/or as the usual accompaniment of damage to the seminiferous epithelium.

Our own studies have achieved best success when preparations of F.S.H. from pituitary glands, and chorionic gonadotrophin were used for stimulating gametogenesis and endocrine function, respectively. Charny[23] has used preparations of pregnant mare serum with success in some instances. In other cases, probably instances of primary testicular failure, the results were negative or uncertain. A major problem which accompanies the use of any gonadotrophin derived from nonhuman sources is the occurrence of antibody reactions which interfere with the active principle when treatment is continued for considerable periods of time. This is not a factor in the case of preparations of chorionic gonadotrophin whose source is human pregnancy urine. There is a need for an F.S.H. preparation derived from human sources. Such a source is available in castrate and menopausal urine and probably will be utilized in the future.

SUMMARY

Testicular biopsy has proved to be of indispensable value in arriving at correct diagnoses of cases of male hypogonadism. On the basis of such studies, together with assays for urinary gonadotrophins and physical findings, it is possible to classify male hypogonadism in two major groups and several subgroups. The major categories are primary hypogonadism, which is the result of some defect of or within the testis itself, and secondary hypogonadism, which is due to insufficient stimulation of the testis by hypophysial gonadotrophic hormones. The minor groups are based upon the age at which the gonadal defect occurs and upon the function of the testis, gametogenic or endocrine, which is involved.

Cases of primary hypogonadism are, with very few exceptions, associated with high urinary levels of gonadotrophin. Treatment of the gonadal deficiencies in such individuals must be confined to the use of androgenic hormone which will stimulate the various secondary sexual characteristics. No endocrine approach for the correction of defective gametogenesis in these patients is available at present since preparations of the gonadotrophic hormones have been ineffective.

Men whose gonadal deficiency is shown to be due to inadequate stimulation of the testes by gonadotrophic hormones (secondary hypo-

gonadism) almost invariably have low urinary levels of gonadotrophin and are benefited by treatment with preparations of gonadotrophic hormone. However, in all instances of secondary hypogonadism, primary attention should be directed toward diagnosing and correcting such conditions as may interfere with normal activity of the hypophysis.

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ENDOCRINE THERAPY IN DISEASES OF THE PROSTATE GLAND

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Of the many diseases that affect the prostate gland, inflammations, hypertrophies and cancers are the most common. In recent years, especially since the investigations of Huggins and his associates in 1941, many observations have been reported on the use of hormones in the treatment of diseases of the prostate.

PROSTATIC CANCER

Although this disease is not the most common affliction of the prostate gland, recent statistics indicate that up to 15 per cent of men beyond the age of 55 develop prostatic carcinoma. In the majority of patients the diagnosis is relatively easy to make; however, in a few it can be difficult and must depend upon a biopsy. But if a patient is past 55 years of age and comes to his physician with complaints of hematuria, difficulty of urination, backache and leg pains, and the rectal examination reveals a hard, infiltrated, nodular prostate, then the most likely diagnosis is carcinoma, because no other disease of this organ produces such hardness.

In the last fifty years, many different forms of treatment have been advocated, and intensive efforts have been made to treat this disease successfully. However, those who have observed a considerable number of patients with advanced carcinoma of the prostate have found little encouragement from any form of therapy. It is definitely agreed by urological surgeons that in early carcinoma of the prostate—that is, when the disease is confined within the limits of the gland itself—radical perineal prostatectomy is the proper procedure. Unfortunately, such a condition is found only in a minority of cases, not over 5 per cent, as compared with the group of patients in which the disease has extended beyond the borders of the gland by the time the patient has presented himself to the physician for relief of his symptoms. The reason for this is quite obvious. Early carcinoma of the prostate, like carcinoma in many other organs, is a silent disease. It is only when symptoms of urinary obstruction develop, or pain from metastases occurs, that the patient seeks relief from his trouble. It cannot be emphasized too frequently that every male patient, regardless of symptoms for which he consults his physician, should have a rectal

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examination. If this is made a routine procedure many more early cancers will be recognized.

Of the many methods that have been used in the treatment of advanced prostatic carcinoma, the endocrine procedure of Huggins and his associates is the most favorable. In general, the results of his investigations show that some types of prostatic cancer are often extremely sensitive to androgens, or the male sex hormone, and the presence of this material in the body activates the growth of the cancer. In many patients, the inactivation of the male sex hormone brings about a retrogression of the cancer cells. This can be accomplished in two ways—by castration, or by the administration of estrogens. These endocrine theories of Huggins have been widely accepted in the treatment of advanced prostatic cancer. It has long been known, for instance, that a direct relationship and interrelationship exists between the glands of internal secretion, especially the pituitary and the gonads, and the function of the prostate. At about the turn of the century, castration was done for so-called benign prostatic hypertrophy, but it was soon discarded because of the poor results. At the present time, there is some difference of opinion as to whether castration or the administration of estrogens will accomplish the same clinical response in patients with prostatic cancer. It is well established that in experimental animals castration increases the gonadotropic activity of the anterior lobe of the pituitary, and it is known that the production of androgens is under the influence of this principle.

Furthermore, it has been demonstrated that other organs besides the testes, notably the adrenals, are capable of producing androgens. Therefore, castration would not inactivate all the androgens, but might even increase the production of androgens in other organs. On the other hand, the administration of estrogens is believed to inactivate the production of androgens by depressing the gonadotropic activity of the pituitary. If this be true, then this form of therapy would be more likely to inactivate the production of androgens in all parts of the body. However, up to the present time, numerous clinical reports have failed to demonstrate definitely that the administration of estrogens produces a better response in the patient than castration. It will be interesting, after a longer time has elapsed, to compare the ultimate results of these two forms of therapy in cancer of the prostate.

Phosphatase Determinations in Diagnosis and Treatment.—Another recent development in the diagnosis and treatment of prostatic cancer is the estimation of the amount of certain enzymes that are present in the body. These are known as acid and alkaline phosphatases. Alkaline phosphatase is found in growing bone, particularly in the osteoblasts. It is also found in the convoluted tubules of the kidney, and is said to be abundant in the surface epithelial cells of the mucosa of the upper part of the intestine. It is also present in many other organs in smaller amounts.

Acid phosphatase is likewise found in many organs, especially in the erythrocytes and in the parenchymatous cells of the prostate. Both alkaline and acid phosphatase are present in the blood serum, and can be determined quantitatively by chemical means and in tissues they can be rendered visible by microtechnical stains. This laboratory procedure is now not only widely employed as an aid in the diagnosis of advanced prostatic cancer, but also as a yardstick in the interpretation of the efficiency of endocrine therapy. The acid phosphatase is increased in carcinoma of the prostate gland with metastasis, especially if the cells are well differentiated. On the other hand, highly undifferentiated prostatic cancer produces very little of this enzyme, and therefore the serum acid phosphatase may be normal even with extensive metastasis. Although the alkaline phosphatase is likewise increased in advanced prostatic cancer, other diseases, especially of the bone, such as Paget's disease and osteogenic sarcoma, will also produce an increase of this enzyme. There are apparently some limitations of the value of this diagnostic method, and as yet these limitations have not been too clearly defined.

Response of Advanced Prostatic Cancer to Estrogenic Therapy.—No effort will here be made to compare the efficiency of estrogenic therapy with that of castration. It has been our experience that estrogenic therapy is as beneficial, and the results as good, as those obtained by orchiectomy. In a previous communication, we reported fifty patients with advanced prostatic cancer who had been treated with diethylstilbestrol. The youngest was 52 years of age and the oldest 81 years at the time they were first seen. No patient was included in the report who had not been observed for at least six months. Of the fifty patients, twenty-four were previously reported in 1944. At that time it was observed that six patients, or 25 per cent, died from the disease during the time they were under treatment; four patients, or 16.6 per cent were not improved; and fourteen patients, or 58.4 per cent, had been definitely benefited by this form of therapy; i.e., they had been relieved of their pain, their appetites improved, anemia disappeared, their weight increased, and all had the appearance of well being and good health. Of the twenty-four patients, at the present time eight are alive and clinically in good health; they have normal weights, no pain

TABLE 1

SURVIVAL AFTER ESTROGENIC THERAPY—25 PATIENTS

Length of Time Observed	Number of Patients
6 months to 1 year	1
1 year to 2 years	9
2 years to 3 years	4
3 years to 4 years	4
4 years to 5 years	3
Over 5 years	4

or discomfort, their appetites are good, and they are all living a normal life. Four of the eight patients, whose ages vary from 76 to 87, have been observed for over five years. Three patients of the twenty-four, ages 81, 84, and 87 respectively, are alive but incapacitated with other diseases—two from cerebral thrombosis and one, the oldest, from senile dementia. Two of the twenty-four are alive and suffering from pains and symptoms of prostatic metastasis. Ten are now dead, and of the one remaining, we do not have a report.

TABLE 2

RESULTS FROM ESTROGENIC THERAPY—50 PATIENTS

Improved	25 patients
Dead	20 (18 from disease)
No improvement	3
Not known	2

TABLE 3

SURVIVAL AFTER ESTROGENIC THERAPY (FIVE YEARS AND OVER)—4 PATIENTS

Present Age	Before Therapy			After Therapy		
	Prostate	Metastasis to Bone	Operation	Prostate	Metastasis to Bone	General Condition
76	Hard, nodular Extensive periprostatic spread	No	Transurethral two times	Softer, smaller	No	Very good
80	Hard, nodular	No	No	Somewhat softer	No	Very good
78	Hard, nodular Perioprostatic spread	Yes	Radical perineal	Soft	Yes	Very good
87	Hard, nodular	No	Transurethral	Somewhat softer	No	Poor; senile dementia

In analyzing the fifty patients as a group, we find that twenty-two are alive and enjoying good health, twenty are dead, and three are alive and suffering with the disease, three are alive and suffering with other diseases, and two cannot be traced. The term "good health" denotes the disappearance of pain, gain in weight, disappearance of anemia, increased appetite, and a general state of well being. The prostate and the periprostatic extension of the cancer have become softer, and in many cases, smaller. The histological changes that occurred in the prostate were very striking and pronounced. The altera-

tions are characterized chiefly by extensive hydropic degeneration of the cancer cells. In this series, there was no instance in which the metastasis to the bony structure had completely disappeared.

It has been our method to use 1 mg. of diethylstilbestrol three times a day by mouth, although in many patients much larger doses, up to 25 mg. a day, were given. The diagnosis of advanced prostatic cancer was made from rectal findings, x-ray findings of metastasis and, usually, histological sections of the prostatic tissue which were obtained before estrogenic therapy was started. It should be recognized that it will do little good to castrate, or to prescribe estrogens to a patient with advanced prostatic cancer, and then let him die from renal insufficiency caused by chronic retention of urine from prostatic obstruction. It is quite obvious that the obstruction must be removed, and this can best be done, in most instances, by a transurethral resection.

In this series of fifty patients, many presented a pathetic and sorrowful picture. Pain was the predominant symptom. Loss of weight, difficulty in voiding, frequency, urgency, pyuria, dysuria and hematuria were common complaints. A few were bedridden and required morphine for the relief of their pains. Two patients had had a radical perineal prostatectomy.

Following the administration of the diethylstilbestrol, the most striking and spectacular improvement was the disappearance of pain, the gain in weight and an increase in appetite. However, it should be emphasized that this improvement did not occur in all the patients. There were twenty-one patients in the series in whom it was observed that very little, if any, benefit resulted from this form of therapy.

Untoward Effects during Treatment.—These were mild and of no importance compared to the clinical improvement that occurred. We have previously shown that in the human impotence, sterility, gynecomastia and complete disappearance of semen takes place during the administration of diethylstilbestrol. We have also observed increased pigmentation, especially of the nipples and on the ventral surface of the penis. Occasionally, leg cramps would occur. Although there have been isolated reports of liver damage from the use of large doses of this material, there was no evidence of this complication in this series of patients. There was one patient who developed severe gastrointestinal symptoms, characterized by diarrhea and pain, following the administration of 25 mg. of diethylstilbestrol a day, but these symptoms disappeared after the hormone was discontinued.

Case History.—The following abstract of a case history of one of the patients with advanced prostatic cancer summarizes the results from this form of therapy:

> J. S., aged 52 years, a white man, was first seen in May, 1938, at which time he had an acute retention of urine, caused by an enlargement of the prostate gland.
>
> A transurethral resection was done. There was no evidence of a malignancy. In

June, 1942, he was seen because of a return of his urinary symptoms. The residual urine was 120 cc. A rectal examination revealed a very hard, nodular prostate gland. He re-entered the hospital for a transurethral resection. The histological sections of the prostate showed a poorly differentiated adenocarcinoma, grade III. X-rays of the spine, pelvis and chest revealed no evidence of skeletal metastasis. In June, 1942, he was placed on 3 mg. of stilbesterol a day and he has remained on this dose continuously to the present time, except for an occasional rest period of three weeks, twice a year. His last examination in September, 1947, revealed the prostate to be smooth and soft. There were no areas of hardness or nodules. He is overweight, and his appetite is good. He has not missed a day's work as an executive in a very busy corporation, nor has he had any complication or side effect from the stilbestrol. He will be advised to continue this form of therapy indefinitely.

Present Status of Estrogenic Therapy.—When should estrogen therapy be started? How much should be given, and how long should it be continued? There is a difference of opinion regarding these questions, and at the present time they cannot be definitely answered. It seems logical that treatment should begin as soon as the diagnosis of prostatic cancer is adequately established. Whether the patient with early prostatic cancer, in whom a radical perineal prostatectomy has been performed, should also be treated with estrogens is still an open question. Obviously, if the cancer has been completely removed, and no metastasis has occurred, the administration of estrogens would serve no purpose. However, there is no method at the present time, including the phosphatase test, that can accurately determine the presence or absence of early metastasis.

The optimum dose of estrogenic hormone that should be given is not definitely known. At least 3 mg. of diethylstilbestrol a day has been advocated by some. It would appear that the amount to be used might depend upon the extent of the carcinoma. We have been of the opinion that much larger doses are more efficacious in the treatment of patients in whom the metastasis is extensive.

Also, it is not known how long treatment should be continued—possibly indefinitely—provided no serious reactions arise; even then it could again be given as soon as the welfare of the patient permits. However, the answer to these questions is still debatable. More time is necessary before a definite statement concerning the amount of hormone, length of treatment and proper time to begin treatment with this form of therapy can be made. There are many more questions that cannot be answered at the present time. For instance: Is castration a better procedure than the administration of estrogens? Should castration be done and estrogens also be given? What are the therapeutic effects in relation to the grade or differentiation of the cancer? Further clinical observations will eventually give the answer to many of these important questions.

At the present time it can be stated that patients with advanced prostatic cancer will live longer and more comfortably with this form

of therapy, or orchiectomy, than all other methods of treatment that have previously been used in this condition. For comparison, it is of interest to review the report of Bumpus, who in 1926 analyzed a thousand patients with carcinoma of the prostate who were observed at the Mayo Clinic. Four hundred and eighty-five cases in the series had no form of treatment, and the average duration of the disease, from the first symptom to death, was thirty-one months. When metastasis was present at the time of the examination, two-thirds of the patients died within nine months. In the group in which examination indicated that metastasis had not occurred, the average subsequent length of life was about a year, but 58 per cent of the patients died within that time. There were four patients in the untreated series of patients who lived more than three years, and two who lived more than ten years.

The Results from Orchiectomy in the Treatment of Prostatic Cancer.— The literature relative to bilateral orchiectomy in the treatment of this disease is now fairly extensive. For instance, Parlow treated seventy-five cases of advanced cancer of the prostate by this method. Eighteen of the patients, in addition, had prostatic resections. The diagnosis was confirmed by microscopic studies in sixty-six cases and in the remaining by x-ray and rectal examination. In twenty-three of the patients, there was no clinical or x-ray evidence of metastasis. The results from the orchiectomy showed that eighteen patients derived no benefits; that is, there was no relief of pain and the progression of the disease was in no way altered. To this group of failures, stilbestrol was administered and proved of no value. Fifty-seven patients manifested an immediate clinical improvement. This was characterized by loss of all metastatic pain and a general improvement in their subjective symptoms. However, forty-three of these were delayed failures in that again the patients developed symptoms of advanced prostatic cancer after an interval from eight to thirty months. It was observed that complete regression of the prostatic cancer occurred only in those patients in whom the prostatic tissue revealed typical adenocarcinoma.

Emmett analyzed his observations in a group of 220 patients who had advanced carcinoma of the prostate treated by bilateral orchiectomy; 164 of the patients revealed evidence of metastasis, 56 were considered to be free from any evidence of metastasis. Of the 164 patients who had metastasis, 127 complained of pain, and 60 per cent of these experienced relief of the pain soon after the operation; 22 per cent were given some relief. However, in many cases the relief of the pain was only temporary. In an analysis of seventy-six cases in which there was an immediate relief of pain after orchiectomy, there was, in a majority, a recurrence of the pain within a few months. Only a small number of patients remained comfortable more than a year. It is of interest that in 132 patients with metastasis on whom phosphatase studies were made, the serum acid phosphatase and serum alkaline phosphatase levels of 35 were normal.

Still another report is that of Nesbit, who in 1944 reported a follow-up study on seventy-five patients with prostatic cancer whom he had treated by bilateral orchiectomy. There was no case in this series in which twenty-one months had not elapsed since the operation. All the patients except four had an infiltrating carcinoma. Forty-three were suffering from pain, cachexia or other clinical manifestations of advanced carcinoma. His results showed that ten patients received no benefit from the operation, five died within six months, four died within fifteen months, and one was alive twenty-two months after the castration. There were sixty-five patients who were improved clinically, but many of these derived only temporary benefit. He could establish no criteria in predicting the prognosis. He

divided his series into two groups: *Group I.* The thirty-two patients, including those in whom there were no symptoms of advanced prostatic cancer. In this group, twenty-two patients were alive and well. *Group II.* The forty-three patients who had pain, cachexia or other complaints referable to the disease. Twelve of this group were alive and well. Nesbit is of the opinion that treatment should not be given either in the form of estrogens or castration until the signs and symptoms of advanced carcinoma have developed.

Dean reported that in his clinical experience with the endocrine treatment of prostatic cancers, in which 100 cases were studied, forty were observed for only short periods, or were lost to follow-up, and of the remaining sixty, who were observed for six months, or more, thirty-one were treated by surgical castration and twenty-nine by stilbestrol. He stated that surgical castration almost invariably gave prompt relief, and in no case was orchiectomy withheld because of advanced disease, although many patients seemed near death at the time of the operation. Frequently, patients learned to walk within a few days after the operation and, almost without exception, pain disappeared within forty-eight hours. In a number of instances, metastasis in the lungs could no longer be demonstrated a short time after treatment. However, after a short period of apparent good health, which on the average lasted eight months, the majority of the castrated patients relapsed. While the great majority of castrated patients improved, a small percentage died a short time after operation. Dean further observed that in a large proportion of his patients who suffered relapses following castration, and who were treated with stilbestrol, some improvement was noted, though it was not as sudden as that which followed castration. However, the majority seemed as well as those who had benefited most by castration. In a group of twenty-three patients treated with stilbestrol, he found changes in acid serum phosphatase similar to those which followed castration. He concluded from his studies on assays of estrogen and androgen excretion levels in a group of patients who had been castrated and in another group who were given estrogens, that the mechanism whereby castration and stilbestrol cause regression of prostatic cancers is fundamentally different.

In 1945, Scott and Benjamin reported on eighty-two consecutive patients with various stages of development of prostatic carcinoma. The average age of the patients was 69.4 years, with a range of 55 to 84 years. In 83.5 per cent of the cases the growth was predominantly adenocarcinoma, while in 16.5 per cent it was undifferentiated. Sixty per cent of the patients in the latter group and 26.7 per cent in the former were known to be dead at the completion of the study. Serum acid phosphatase studies were made on seventy-six of the eighty-two patients, thirty-seven of whom had normal preoperative readings, and in thirty-nine the level was high. The authors observed that regression of the disease occurred in 54 per cent of the patients; 26 per cent of the patients showed no change; in 2 per cent the cancer progressed; and 17 per cent could not be followed. A transurethral resection for relief of urinary obstruction was necessary on thirty patients following orchiectomy.

One of the most recent reports is that of Huggins, who summarized his observations on twenty patients who had been observed for five years since they had their orchiectomy. He now has four patients in whom no sign of the disease can be detected. They all had elevated serum phosphatase and widespread metastases before the orchiectomy was performed. In these four patients, five years afterwards, the phosphatase levels are within normal range, and the bones show no evidence of metastasis. He states that two factors are of significance in determining the effectiveness of orchiectomy: (1) the tumor must be androgen dependent, and (2) the testes must contribute functionally significant amounts of the total amount of androgen. He feels that this form of treatment is superior to the neutralization of the androgen by the administration of estrogens.

Although we have observed some patients in whom orchiectomy produced a better response than had previously been produced by estrogens, we likewise have

observed an equal number of patients who have received a better response from the use of estrogens than they previously had from orchiectomy. Before any definite statements can be made relative to the merits of castration over estrogenic therapy, or vice versa, more clinical investigation and evidence is needed.

BENIGN PROSTATIC HYPERTROPHY

This is a common disease in elderly men. Statistics show that up to 55 per cent of men who reach the age of 60 years will develop some signs and symptoms of prostatic obstruction. About 50 per cent of these men will eventually need to have this obstruction removed by a surgical procedure.

However, recently, enthusiastic results from the use of estrogens have been reported. Although it has been adequately demonstrated that the estrogens produce extensive histological changes in the glandular structure of the prostate gland, yet, in our experience, we have not been impressed by the beneficial results from the use of this material in the treatment of patients with benign prostatic hypertrophy, as the urological surgeon recognizes it. Whether estrogenic therapy will offer relief to patients with so-called beginning prostatic enlargement is problematical. More clinical observations and reports are necessary before any clear-cut statements can be made.

Clinical Response to Estrogenic Therapy.—We have previously reported our results in thirty-three patients with benign prostatic hypertrophy who were treated with diethylstilbestrol. The criteria used to establish the diagnosis of prostatic enlargement are those well known to all urologists, i.e., history, rectal examination, cystoscopy and the estimation of residual urine. The diethylstilbestrol was given by mouth, usually 1 mg. three times a day, although up to 10 mg. a day was given to a few patients. The patients fell into two groups:

Group I was comprised of twenty-seven patients who had the signs and symptoms of early prostatic obstruction. The prostate gland was enlarged from 1 plus to 2 plus, and the residual urine varied up to 60 cc. The cystoscopic examination revealed definite obstruction around the neck of the bladder in the form of lateral lobe hypertrophy, middle lobe enlargement, or both. No patient was included, no matter how severe his urinary symptoms, unless the cystoscopic examination showed definite evidence of prostatic enlargement. The average age of the patients in group I was 63.49 years, the youngest 50 years, and the oldest 75 years. They were treated from 28 to 498 days, receiving the hormone in amounts ranging from a minimum of 54 mg. to a maximum of 1320 mg.

The results of the therapy can be discussed under two headings: (1) the decrease in the size of the prostate and (2) the improvement in the urinary symptoms. In seven patients, it was believed that the prostate had decreased slightly in size. There were five patients in whom the urinary symptoms of day frequency, nocturia, hesitation,

dribbling and difficulty in starting the stream were lessened. However, two patients in whom the urinary symptoms improved showed no sign of change in the size of the prostate per rectum. We could not demonstrate by cystoscopic examination any decrease in the size of the prostate in any of the patients following treatment.

Group II was comprised of six patients, the youngest 63 years of age, the oldest 75 years, and the average age was 71.16 years. Their residual urine varied from 60 cc. to 1000 cc. The prostate gland was enlarged from 2 plus to 4 plus. They received treatment from 49 days to 456 days, receiving from 200 mg. to 1774 mg. Five in this group were hospitalized; in four the obstruction was relieved by transurethral resection, and in one a suprapubic prostatectomy was necessary. Of the five patients who were hospitalized, the prostate gland was thought to have decreased in size in three patients. However, all the patients did not completely empty their bladders, and the symptoms of urinary obstruction still persisted. No change in the size of the obstruction following treatment could be observed by cystoscopic examination.

Present Status of Therapy.—Although the estrogens produce improvement in the urinary symptoms in some of the patients, it must be remembered that many patients with prostatic obstruction will show similar improvement from the use of sitz baths and alkalies. On the other hand, the administration of estrogens in contrast to androgens produces extensive degenerative changes in the glandular structure of the prostate, which no doubt is responsible for the decrease in the size of the gland observed in some patients. However, these alterations are only temporary. When the estrogen is discontinued, the glandular structure again regenerates. Also in patients with a high residual urine, this form of therapy has given only partial relief at best. It would seem, therefore, that estrogenic therapy is not the treatment of choice in prostatic enlargement as the urological surgeon recognizes it, that is, symptoms of urinary obstruction, residual urine, and an enlarged prostate per rectum. The treatment still rests with the old and well established surgical procedures.

INFECTIONS AND OTHER CONDITIONS OF THE PROSTATE GLAND

Although several reports have been presented in the literature to the effect that hormonal therapy is efficacious in the treatment of prostatic infections, more well controlled observations are necessary before this form of treatment can be advocated in this disease. However, there are several well recognized diseases which many times are thought to be caused by inflammation of the prostate, in which estrogenic therapy is of distinct value, one being premature ejaculations.

Premature Ejaculations.—These may or may not be associated with poor erections. It is one of the most common sex complaints in young men. If severe, it can be responsible for a sterile marriage. The causes are many. Local inflammatory lesions such as prostatitis with a

posterior urethritis may be responsible. If the condition is not associated with poor erections, the administration of small doses of diethylstilbestrol, 0.5 mg. per day for six or eight weeks, has proved efficacious in many instances. However, it should be used cautiously because a man can be made temporarily completely impotent from its use.

Hematospermia.—Another less common disease is hematospermia which is characterized by bloody semen. Since most of the seminal fluid is made up of prostatic fluid, it is thought that the blood comes from the glandular portion of the prostate. We, as well as others, have found small amounts of diethylstilbestrol, 0.5 to 1 mg. a day for five or six weeks, to be very efficacious in the treatment of this condition.

CONCLUSION

Of all the diseases of the genitourinary system for which estrogenic therapy is advocated, it would now seem that its greatest field of usefulness is in the treatment of advanced prostatic cancer.

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CRETINISM

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CLASSIFICATION OF CRETINISM

Cretinism is thyroid deficiency and was first classified by Pineles as follows: (1) congenital athyreosis or sporadic cretinism; (2) endemic cretinism; (3) infantile or childhood myxedema.† To this may be added (4) congenital goiter with cretinism. It is possible the etiology of the latter may be similar to that of endemic goiter.

Congenital Athyreosis or Sporadic Cretinism.—In this disorder the infant is apparently born without a thyroid gland, but on careful search a few follicles of thyroid tissue[8, 9, 13, 27, 28] have been found. At birth these infants may appear normal, are usually of normal length and weight and there are few, if any, other physical changes which can be detected. They nurse poorly, fail to cry frequently and sleep a good part of the time. Recognition of this disorder at this time is of great importance since the effects of little or no thyroid secretion appear to create more irreversible changes, particularly in the nervous system, than at any other period in life (Fig. 28).

Endemic Cretinism.—A thyroid deficient child who is born with an enlarged thyroid gland is generally considered to be an endemic cretin particularly if birth occurs in a region where goiter is common. If this happens outside the endemic region it is at times difficult to explain, and since several members of the same family may be so affected,[22] the term "congenital goiter" is used (Figs. 29 and 35). From a clinical viewpoint, this differentiation is not important because the subsequent course is similar.

Cretins with goiter, as a rule, are not as profoundly deficient in thyroid secretion so that their skeletal as well as mental development is not always greatly retarded.[9] In endemic goiter regions cretinism is often associated with various nervous system defects, such as feeble-mindedness, speech impairment, deafness or deaf-mutism.[9] In India, cretinism associated with parathyroid deficiency and tetany has been described.[30]

Thompson[40, 41] and others have shown, too, that thyroid deficient patients without palpable thyroid tissue will not respond to the injec-

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† If the term *cretinism* is used as above, it should be applied to all cases of thyroid deficiency up to the cessation of longitudinal growth which is the only logical dividing line between youths and adults.

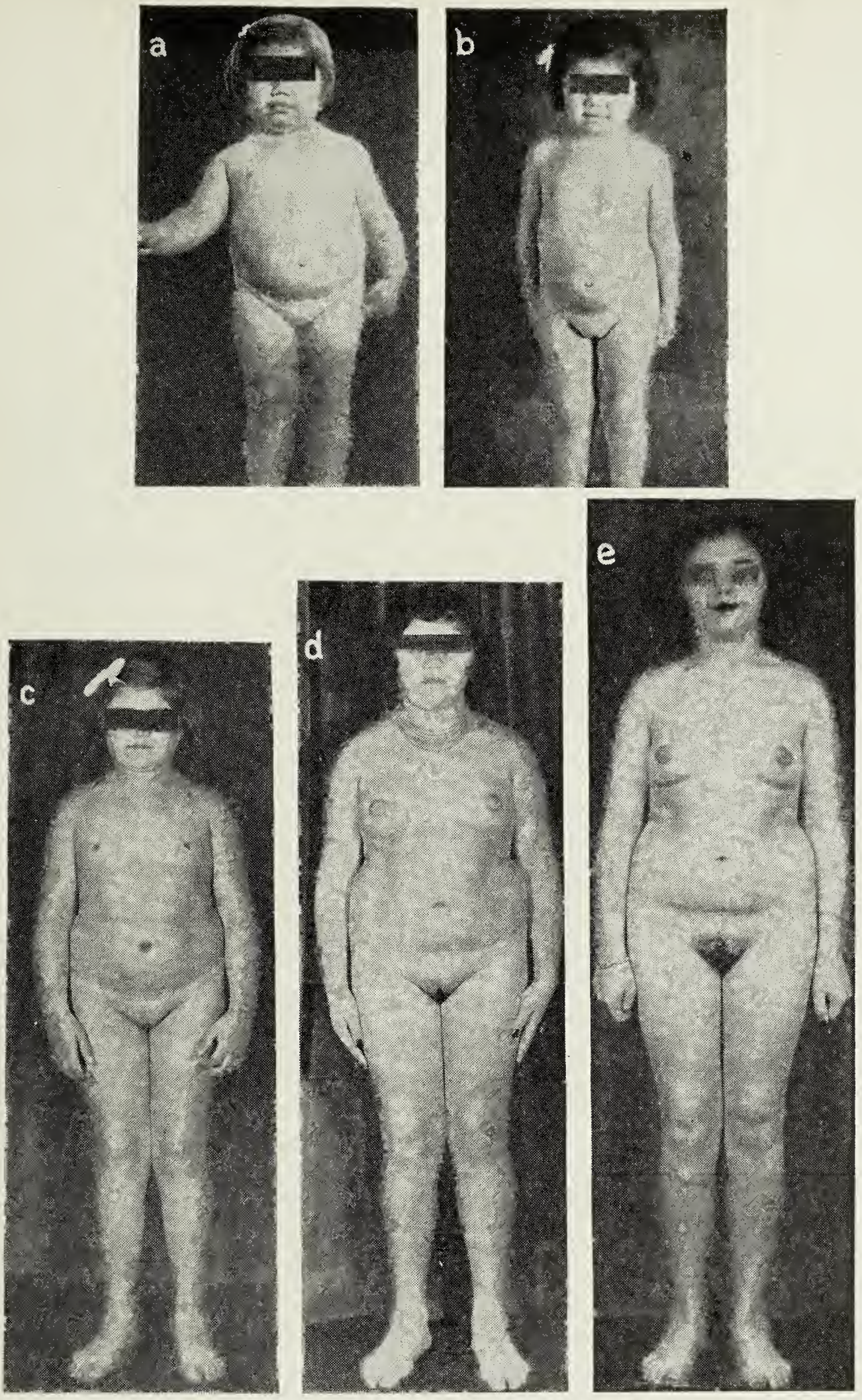


Fig. 28.—Cretinism; infantile myxedema or congenital athyreosis. *a,* At 7 years when adequate treatment was begun. Patient received inadequate and irregular treatment previously. Unable to walk unaided. Marked flat feet and lumbar lordosis. *b,* Three months later, *c,* At 12 years. *d,* At age 16 the patient had not taken thyroid for some months. *e,* Final result: normal intelligence, height age retarded, radial epiphyses closed at 18 years of age. Sella measured 9 by 13 mm. at 7 years and 11 by 14 mm. at 18 years. Blood cholesterol when first observed, 460 mg. per 100 cc.; basal metabolic rate — 26 per cent; bone age of 9 months at 7 years of age strongly indicates congenital athyreosis. It is believed that the early although inadequate treatment in infancy was responsible for the normal intelligence attained. (**From Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1:*72 [July] 1946.**)

tion of thyrotrophic hormone, whereas those with normal glands or with goiter often responded. As long as there is reactive thyroid tissue present in endemic cretins with goiter there may be a partial or complete return of thyroid function and in some cases an excess (Fig. 30). It is possible, therefore, for a cretin with endemic goiter to recover from thyroid deficiency which may have lasted for some years and subsequently develop a state of hyperthyroidism. When the latter takes place, or even when normal function is recovered, there is usually a

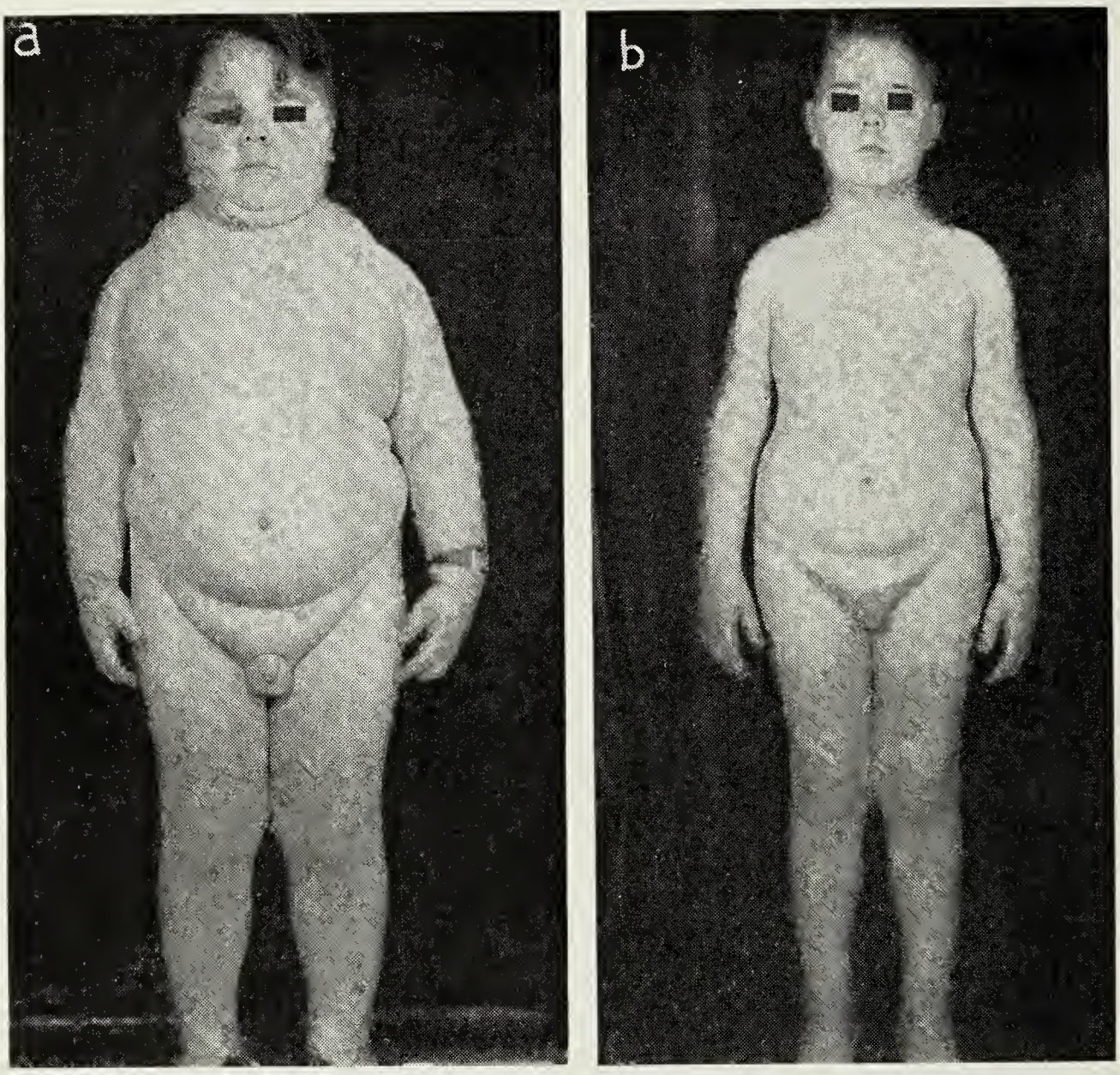


Fig. 29.—*a,* Cretin, aged 14, with substernal goiter (congenital) and concurrent thyroid deficiency before treatment. Basal metabolic rate, — 36 per cent; blood cholesterol 360 mg. per 100 cc. *b,* After fourteen months' treatment. (From Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1*:66 [July] 1946.)

marked spurt in growth and an increase in mental and physical activity.

Infantile or Childhood Myxedema.—Infantile or childhood myxedema may begin very early in infancy, thus making it impossible to distinguish it from congenital thyroaplasia (Figs. 31 and 34). It is probable that most infants developing myxedema would have behaved fairly normal during the first year or so of life. Differentiation might be possible by observation of bone age, which will be discussed later.

ETIOLOGY OF CRETINISM

Congenital Athyreosis.—As stated above, although these infants have no palpable thyroid gland, small amounts of follicular tissue may be found in the region of the thyroid or even at the base of the tongue; their appearance does not suggest a disease process and the cause is generally considered to be a defect in embryologic development. Some infectious or toxic process specifically selecting the thyroid in early embryonic life is possible.

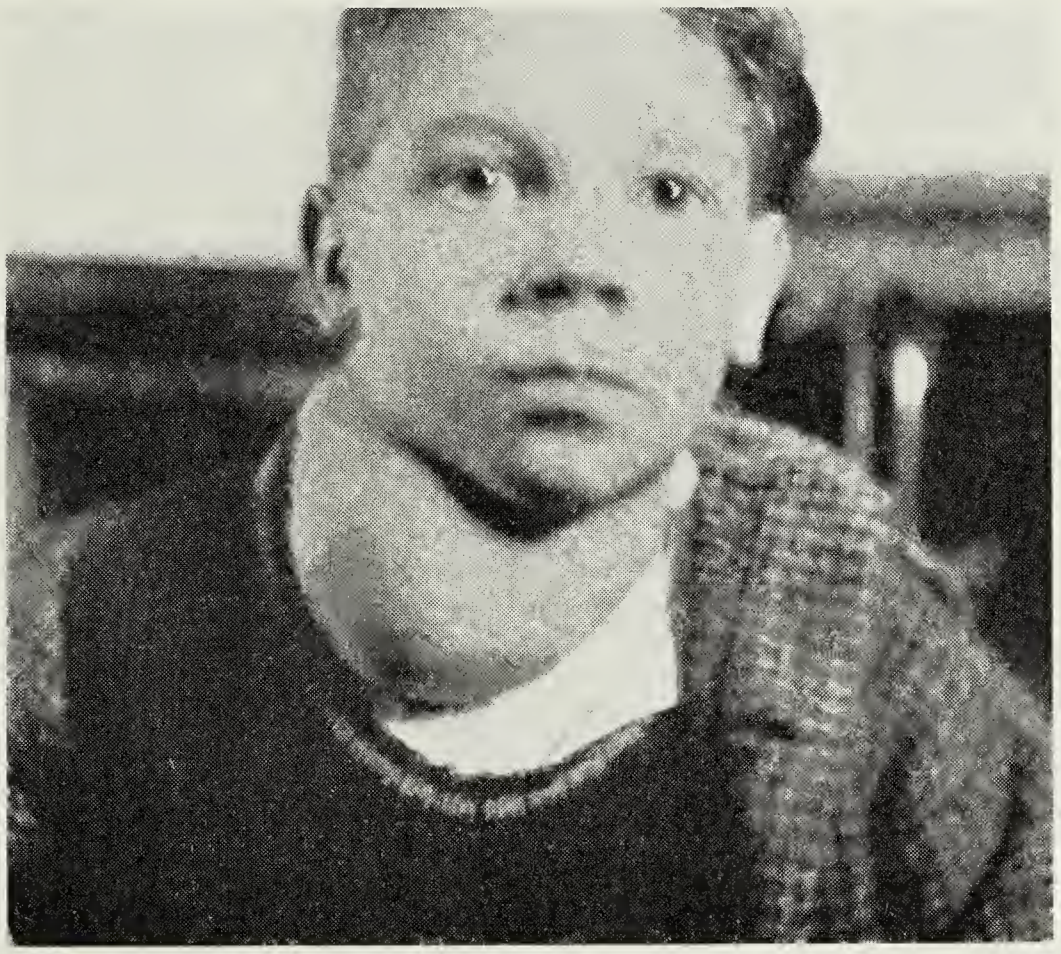
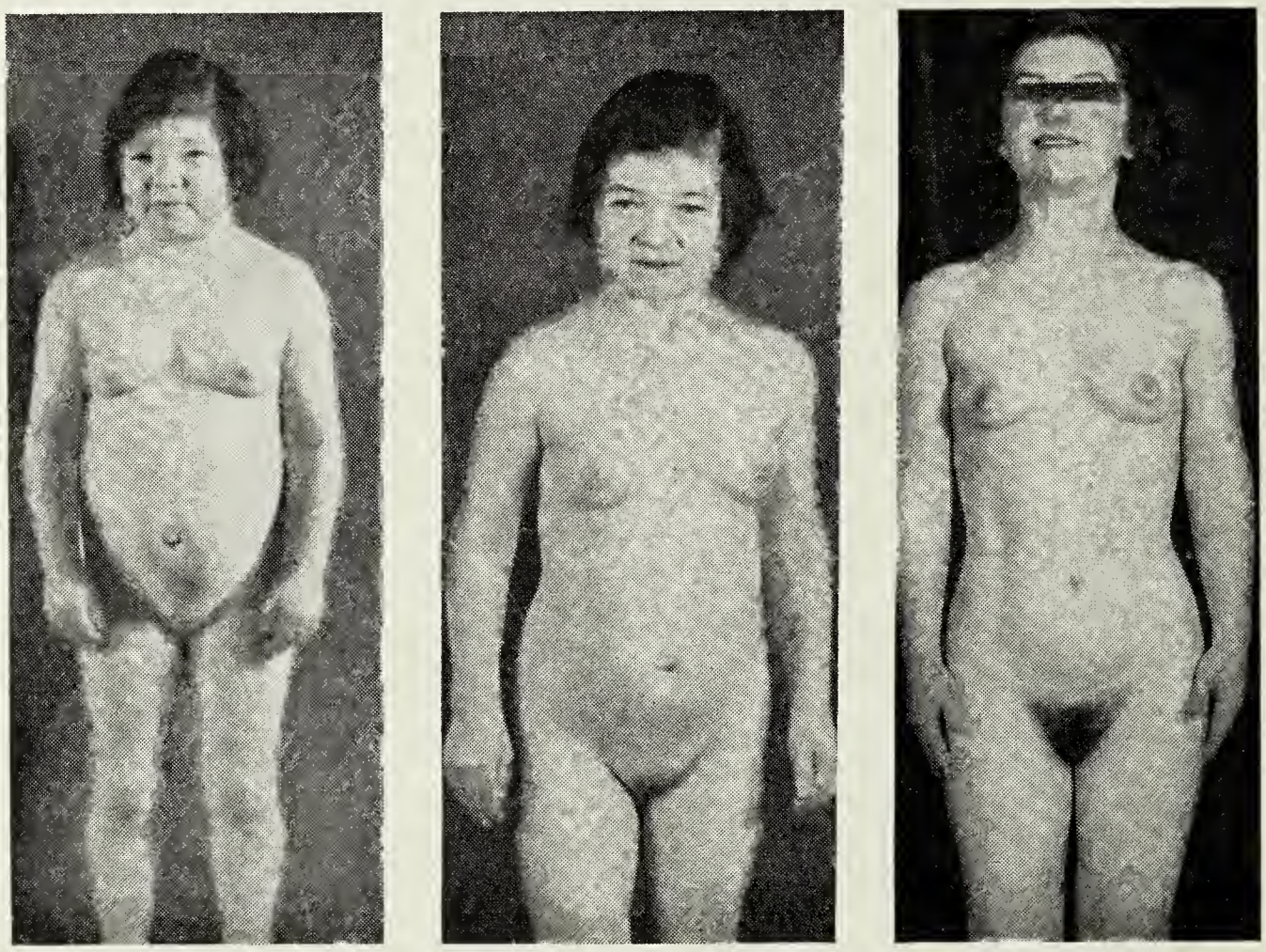


Fig. 30.—Cretinism with concurrent euthyroidism and subsequent hyperthyroidism. Boy, aged 11, height age 7 years, bone age 5 years. Mentally alert, no evidence of concurrent thyroid deficiency. Basal metabolic rate + 12 per cent, blood cholesterol 212 mg. per 100 cc. The goiter had increased in size before admission and there had been an improvement in growth rate, mental and physical activity. The retarded height age and bone age are stigmata of previous thyroid deficiency. After subtotal thyroidectomy, desiccated thyroid was prescribed, which was taken for several years. At age of 22, patient returned with recurrence of goiter and hyperthyroidism (basal metabolic rate + 32 per cent). First pathologic report, colloid adenomatous goiter. Second report (at age 22), colloid adenomatous goiter with areas of hyperplasia. (From Bartels, E. C.: Hyperthyroidism Developing in a Cretin. S. Clin. North America, 25:676 [June] 1945.)

Endemic Goiter.—The cause of endemic cretinism is identical with that of endemic goiter. The theory of iodine deficiency in the diet or water has had many supporters, yet it cannot be proved with certainty to be the primary cause. Greenwald[18] believes that iodine, when administered to children in goiter areas, acts purely as a pharmacologic agent rather than supplying the deficiency. McCarrison[30, 31] has shown experimentally that there may be multiple causes for goiter and that it

may develop in regions where the water supply is adequate in iodine. It would appear then from his work, as well as the work of many others, particularly Chesney, Clawson and Webster,[7] and Mackenzie, Mackenzie and McCollum[29] that the active agents producing goiter are numerous, and that some of them occur naturally (cabbage, alfalfa, mustard seeds, nuts, corn, bran, etc.). Even antigoitrogenic agents may be found in these articles. Familial predisposition to acquire goiter is also frequently discussed and may be an important factor in etiology.



A *B* *C*

Fig. 31.—Cretin, aged 18. Irregularly and inadequately treated; onset in infancy; no palpable thyroid; presumably congenital athyreosis. *A*, Before institution of adequate therapy. Basal metabolic rate — 18 per cent; blood cholesterol 430 mg. per 100 cc.; bone age, 11¼ years. *B*, After three months of treatment; 10 grains of desiccated thyroid per week. *C*, After one year of treatment. Height 49½ inches at 18; two years later, 53½ inches. Pregnancy occurred later with normal baby. For bone changes see Fig. 32. (From Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1*:67 [July] 1946.)

Goitrogenic agents may produce goiter by preventing the manufacture of thyroid hormone through their effect on the enzymic system or by preventing the adequate intake or liberation of iodine by or within the thyroid gland itself. Other possibilities, however, have to be evaluated, such as the interference with the bodily absorption of iodine, although the intake may be adequate, and vitamin as well as nutritional deficiencies which may predispose to the development of goiter with or without the effect by goitrogens. Infective agents may work

either directly upon the thyroid gland or by interfering with the adequate absorption of iodine and vitamins from the intestinal tract.

Infantile or Childhood Myxedema.—There is little information regarding the findings in the thyroid in this form of thyroid deficiency. Some of the palpable but barely enlarged thyroids have the consistency of colloid goiters and might, therefore, be due to essentially the same causes as endemic goiter. In some the thyroid is very firm and suggests

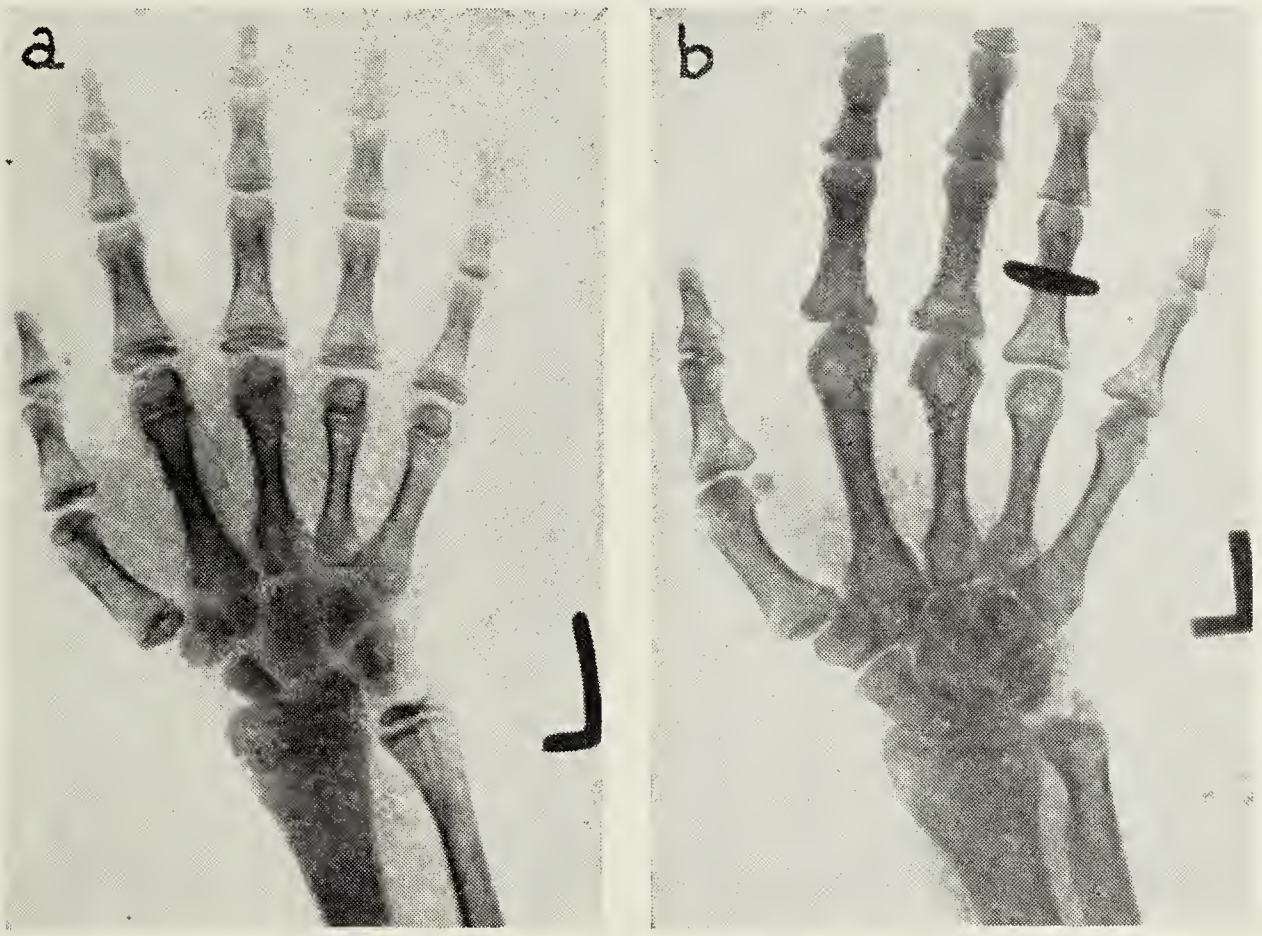


Fig. 32.—*a,* Roentgenogram of hand of cretin 18 years old with concurrent thyroid deficiency in which previous treatment was inadequate. *b,* After three years of treatment resulting in complete epiphyseal closure. Note dense and widened phalangeal bones due to long-standing hypothyroidism. Height age at 18 years was 8 years; at 20, 10 years. Puberty began during the first year of treatment (see Fig. 31). (From Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1*:67 [July] 1946.)

thyroiditis, while in others no definite thyroid tissue can be found. Even with what is known about the production of goiter in animals, there is much obscurity in the cause of most thyroid disturbances in the human.

PITUITARY-THYROID RELATIONSHIP

Before the discovery of thyrotrophic hormone, it was known that some relationship existed between the pituitary and thyroid. Nièpce,[32] in 1851, noted that the pituitary glands of cretins were enlarged to three or four times the normal size. Subsequently, Rogowitsch[35] observed hypertrophy of the pituitary in rabbits after removal of the thyroid gland. These findings have some clinical importance, and will be discussed later. With the discovery of the thyrotrophic hormone,

which stimulates the thyroid epithelium and is the chief regulator of thyroid activity, these earlier observations, just cited, became clearer. Although the thyroid gland has a low level of independent activity it is insufficient to maintain normal bodily requirements of thyroid hormone. This deficiency is the stimulus for pituitary thyrotrophic activity. A hypofunctioning thyroid gland, such as found in cretinism or endemic cretinism, or its removal, stimulates pituitary activity and is thus responsible for pituitary enlargement.

THE FETAL REQUIREMENTS OF THYROID HORMONE AND THE MATERNAL-FETAL RELATIONSHIP

The question as to when the thyroid gland of the fetus actually produces hormone for its own use is not definitely known, but follicles appear about the eleventh week of fetal life[1, 12] and colloid shortly thereafter. Dorff[10] has expressed the belief that the fetus does not require thyroid hormone, at least not until the latter part of gestation. The finding of retarded skeletal development in congenital athyreotics at birth is evidence that thyroid hormone is needed by the fetus in the latter months, at least, of prenatal life. From the available evidence it would appear that the fetus receives only the ingredients for the manufacture of thyroid hormone, chief among which is iodine. Iodine deficiency in the mother from whatever cause would therefore produce iodine lack in the fetus resulting in, during the latter months at least, hyperplasia of its thyroid epithelium and deficiency in thyroid hormone output. Another possibility causing this change and goiter is the excessive thyrotrophic hormone from the mother which is probably transported by the placenta. The causes of excess thyrotrophic hormone in the mother could be due to the presence of myxedema or to the action of goitrogenic agents. The latter, causing goiter in the mother could also produce goiter directly in the fetus, since there is little doubt that these agents, particularly those similar to thiouracil, can pass directly through placental membranes.[3, 16, 17, 19, 20, 38, 44]

To explain the spontaneous improvement in myxedematous mothers during pregnancy or the delay of thyroid deficiency in pregnant animals until parturition, one must seek another reason for such a phenomenon if it is conceded that thyroid hormone does not pass the placental barrier. One possibility is the extrathyroidal production of thyroid hormone. The location of this extrathyroidal synthesis is not known, but the ovary has been suspected.[2, 33] It has not been demonstrated conclusively that the thyroid gland actually synthesizes the finished product which is designated as the thyroid hormone. It is likely that the gland only manufactures the building stones for thyroid hormone which are put together by enzymatic synthesis in the blood stream. If such is the case, one finds it less difficult to believe that this synthesis might also take place under unusual conditions without the aid of the thyroid gland. Nevertheless, it is probably true that most thyroid de-

ficient women cannot react in this fashion or that the mechanism comes into play too late to prevent a miscarriage.

The thyroid deficient mother may become pregnant and give birth to normal children by taking desiccated thyroid. This fact does not mean that the active ingredient of desiccated thyroid permeates the placental membrane, but more likely it supplies the tissues of the mother with adequate thyroid hormone, and so preventing the placental changes that might develop from thyroid deficiency as well as providing adequate iodine for the fetal thyroid when necessary. Furthermore, it probably inhibits excess pituitary thyrotrophic hormone, thus eliminating another possible source of fetal hyperplasia. The administration of iodine to the mother prevents fetal hyperplasia under all known circumstances. It readily passes the placenta.[37]

DIAGNOSIS AND TREATMENT

It has been pointed out that, aside from retarded bone age at birth, or the presence of an enlarged thyroid, there is little physical evidence to arouse suspicion of thyroid deficiency. *In utero* the fetus requires a minimum of thyroid secretion because of its low level of metabolic activity. If the bone age at birth can be used as evidence of thyroid deficiency then there is an unexplained discrepancy in cretins between bone age and the normal proportions in length and weight of the newborn. The need for thyroid hormone after birth increases and if the infant's thyroid is incapable of fulfilling the normal requirements, thyroid deficiency then becomes more manifest.

The first signs by which cretinism can be suspected in infancy are the failure to nurse well, to cry normally, and a tendency to sleep most of the time. The tongue may become enlarged within a few months and some dysphagia invariably occurs. Umbilical hernia, while not a definite sign of cretinism, is often present. There have been few determinations of blood cholesterol shortly after birth, so that it is questionable whether this laboratory aid is helpful in diagnosis. It has been shown that the marked elevation of blood cholesterol, found commonly but not invariably in adult myxedema, may likewise not always be present in cretins. The type of ingested food may be responsible since it is possible to reduce the blood cholesterol in myxedema with a low fat diet. The determination of serum precipitable iodine or organic iodine may be carried out in babies but it requires at least 25 cc. of blood, and is not applicable for use as a routine laboratory procedure. A value below 5 gamma per cent would be expected in cases of thyroid deficiency at this age.[26]

Diagnosis in infancy may, therefore, be difficult. Mongolism is frequently mistaken for cretinism. A Mongol baby, like the cretin, is quiet, does not nurse well and may have other abnormalities commonly found in this disorder. The most characteristic sign is the slant of the eyes. Benda[4] states that the smallness of the orbits is pathognomonic.

The bone age, however, of Mongols at birth is not significantly retarded to the extent found in congenital athyreosis. The roentgenogram of the pelvis and lower ends of the femur do not show centers of ossification; they are, however, present at birth in the normal as well as in mongoloid babies.

The administration of small doses of thyroid is desirable as soon as cretinism is recognized. The use of thyroid as a therapeutic trial during the first few months of life is justified when a real suspicion of cretinism exists. No harm can come if it is used wisely. Initial doses of 4 to 8 mg. ($\frac{1}{16}$ to $\frac{1}{8}$ grain) per day should be sufficient to cause remarkable changes within a few weeks. Doses of 16 to 32 mg. ($\frac{1}{4}$ to $\frac{1}{2}$ grain) should be attempted by the sixth month, and this ought to be increased to at least a grain a day by the third or fourth year.

The diagnosis of cretinism or infantile myxedema in the first few years of life rather than during the first months of life should be a much easier proposition. Failure to grow should lead one to suspect thyroid deficiency. The delay in dentition, swelling of the tongue, and the failure to walk or talk at the usual age are characteristic. A tendency to constipation, dryness of the skin, a bloated or puffy appearance about the eyes are often found.

Thyroid deficiency may show many variations in childhood. As a rule, the untreated children are mentally sluggish. Eventually their mental age falls below normal. Others, although they are few in number, do not have much evidence of mental dullness or retardation. The skin manifestations may not be striking. While many develop a potbelly and have accumulations of fat in the nape of the neck and supraclavicular regions, some may not show these deposits and are actually underweight. The majority, however, are normal or overweight in comparison to their height. Cardiac enlargement[5] and congestive failure[26] with polyserous effusions have been reported in cretinism. The latter is unusually rare. It responds to the administration of thyroid in the same fashion as in adults. Enlargement of the heart shadow in cretinism is probably more frequent than reported. Roentgen-ray studies would undoubtedly reveal a greater incidence.

Osteochondritis is not an infrequent finding in cases of long standing.[11] Hypothyroidism has often been considered the cause of slipped epiphyses in children, but I have not yet observed this phenomenon in a single case of true thyroid deficiency. Flat feet and lumbar lordosis in heavy cretins may produce symptoms, but the latter respond to adequate treatment with desiccated thyroid.

Deciduous teeth[39, 42] are retained much longer than normally and there may be evidence in them of defective development. These abnormalities along with frequent malposition should demand the care of the orthodontist.

The physician who sees an infant fairly often should be the one to

recognize thyroid deficiency early. On the other hand, the disorder may develop so insidiously that the mother or the physician may not realize a change is or has been taking place. If a pediatrician or family physician has not been consulted regularly, thyroid deficiency often has been present for months or possibly several years or more before advice is sought. By this time bone and height ages are two or more years below normal.* The hair is usually fine, fluffy, and may be less than normal. Excess hair about the face, trunk and extremities has been described in a few cases which upon administering desiccated thyroid had decreased in amount.[21, 24] The blood cholesterol is frequently above normal. The basal metabolic rate, if it can be determined accurately, is low.

Since a cretin is commonly a dwarfed person, a consideration of all forms of dwarfism is in order. X-rays of the head should be a routine procedure if there is any doubt about the diagnosis of cretinism. Although Nièpce[32] demonstrated that the pituitary may be three or four times normal in cretinism, this has apparently escaped universal notice.

Enlargement of the sella turcica may be found in most cases of cretinism. In a series of thirty-five cases of all types of cretinism studied by the author,[23] the average of the lateral contour area was normal or increased in all but one case. Routine measurement of anteroposterior and depth diameters showed an increase especially when compared to height age instead of chronological age (Table 1; Fig. 36). This is believed to be due to the compensatory effect of thyroid deficiency rather than a primary tumor of the hypophysis causing myxedema. In borderline cases a very small sella should be evidence against the existence of cretinism.

TABLE 1

AVERAGE MEASUREMENTS OF THE SELLA TURCICA IN THE NORMAL CHILD

(Royster, L. and Rodman, N. F.[36])

Age	*Millimeters*
1– 3 incl.	6.09 by 4.45
4– 6 "	7.74 " 5.44
7– 9 "	8.43 " 6.23
10–12 "	9.36 " 6.18
13–15 "	9.62 " 6.82
16–18 "	11.00 " 10.00

The characteristic response to administered desiccated thyroid is the most convincing proof of thyroid deficiency. Adequate records of height can be obtained from the majority of schools and a graph of previous growth can be drawn. With this in hand there will be little doubt about the acceleration of growth when desiccated thyroid is

* Todd's bone age standards and Burgess height charts are used.

taken. The recovery of the mental and physical activity, the marked drop in blood cholesterol, and the rapid increase in bone age over a period of six months to a year will serve as the final proof for pre-existing thyroid deficiency.

In the dwarfed child who has an enlarged thyroid, there may not be evidences of thyroid deficiency because, as pointed out previously,

Fig. 33.—*A*, Cretin with concurrent thyroid deficiency at 21 months, having begun at 4 months of age and necessitating gastrostomy because of dysphagia; thyroid palpable. Note adenomatous goiter in mother. *B*, Same patient at 12 years. Irregular treatment prior to admission (B. and W. thyroid ¼ grain daily equivalent to ⅒ grain U.S.P.). Treatment thereafter was adequate in dosage but irregularly taken; idiot. (From Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1*:71 [July] 1946.)

thyroid function may have returned to normal. The skin is not dry or cool, the puffiness is gone, the mental dullness will have been replaced by alertness and physical activity returns to that of a normal child. The fat pads and potbelly may have disappeared and bone age may approximate height age by a few years. Upon careful inquiry it is found that the child has had a growth spurt during the past few years

and that the goiter had become larger. The basal metabolic rate and blood cholesterol may be normal. A history of this sort and the finding of a subnormal height age as well as mental age, support the diagnosis of a pre-existing thyroid deficiency (Figs. 30, 35). The term "cretinism with concurrent euthyroidism and past deficiency" may be used in

A *B*

Fig. 34.—Childhood myxedema. *A*, Age 13, duration one year. Chief complaints, languor and weight gain; weight 116 pounds. Height age 12½, bone age 12 years and 3 months. Sella measured 9 by 10 mm. (average normal 9.6 by 6.8 mm.). Blood cholesterol 416 mg. per 100 cc.; hemoglobin 70 per cent; erythrocytes 3,600,000; blood sedimentation rate, 60 mm. in one hour. Thyroid, uniformly enlarged, firm, suggesting thyroiditis.

Patient continued to do well in school despite her lethargy. Dislikes cold weather. Slight secondary sex development, including pubic hair but not catamenia.

B, One year later. Treatment, 1 grain of desiccated thyroid daily. Weight loss of 10 pounds with treatment, then recovered to 109 pounds. Grew 2¾ inches in year (normal rate at this age, 1½ inches). Menstrual periods began after three months of treatment. Blood cholesterol, 176 mg. per 100 cc.; hemoglobin 90 per cent; erythrocytes 4,000,000. Two years later, height 62½ inches. Thyroid normal in size, with only slight firmness. Patient grew a total of 4 inches and changed from 40 percentile curve of Burgess to 60 percentile curve. Weight 116 pounds. Bone age 14.3 years; blood cholesterol 182 mg. per 100 cc.; and sedimentation rate 16 mm. per hour. This case illustrates (1) slight lag in bone age because of short duration of thyroid deficiency and (2) regression of enlarged thyroid.

describing these cases. The administration of desiccated thyroid to such individuals does not cause any improvement, except that in rare instances the goiter may become smaller. The failure to alter the irreversible changes of a long standing thyroid deficiency, which is characteristic of the group, is probably one of the reasons why Euro-

pean authors have believed that endemic cretinism consisted of more than thyroid deficiency.

The same change which may come about spontaneously in endemic or congenital cretins with goiter also takes place in a child who has been given desiccated thyroid. At times it may be doubted that a child who is taking desiccated thyroid daily had a previous thyroid deficiency. The only way to establish a diagnosis when doubt arises is by the discontinuance of the administration of desiccated thyroid. The physical evidences of thyroid deficiency may be slow in appear-

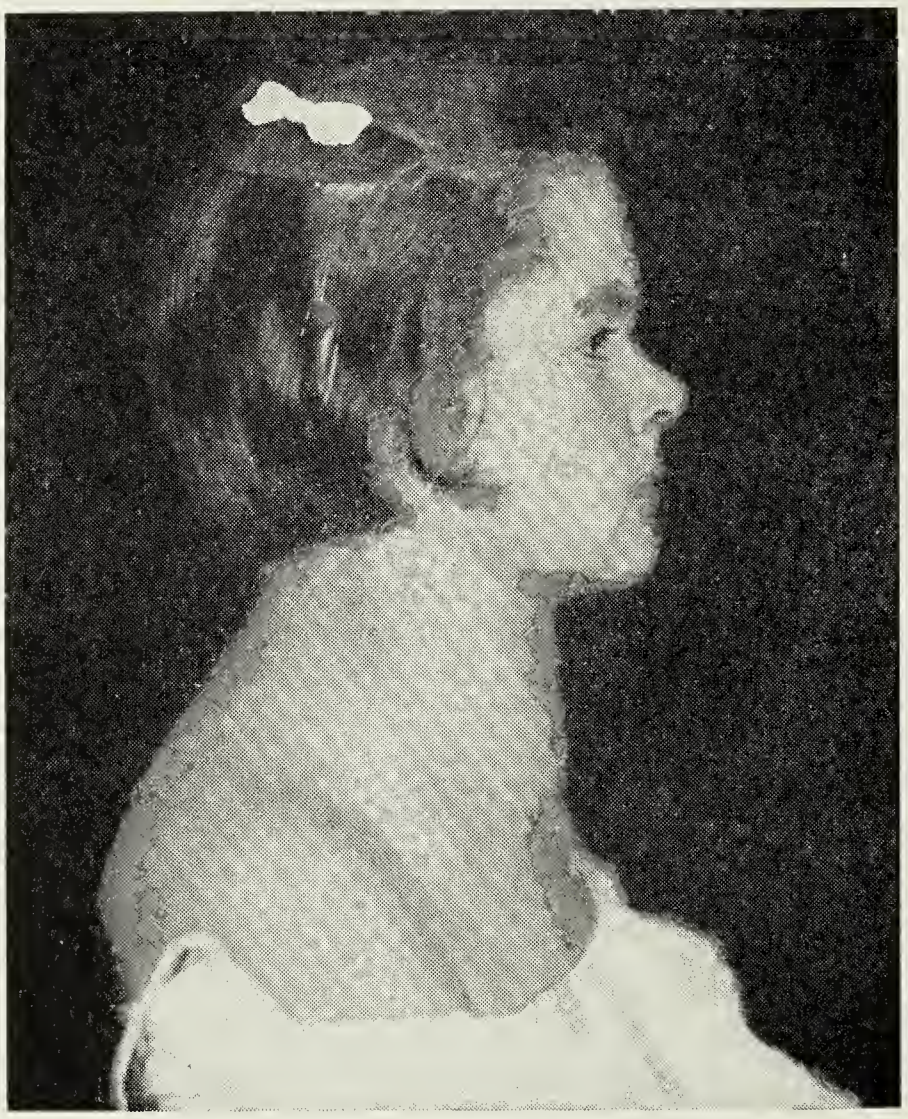


Fig. 35.—Congenital goiter (sister of patient shown in Fig. 29). Previous thyroid deficiency (cretinism) and concurrent euthyroidism (normal thyroid function). Age 20, height age 10¾ years (55 inches). Bone age normal. Catamenia at 17 years of age. Mental status retarded. Basal metabolic rate + 12 per cent. Blood cholesterol 176 mg. per 100 cc. Thyroid deficiency existed during childhood, causing delayed puberty. Function evidently revived around age of 12 to 15 years.

ing, but the basal metabolic rate and blood cholesterol should change within a few months. It has been shown in adults who have been given desiccated thyroid for the treatment of obesity that the basal metabolic rate may fall quickly on stopping treatment.[15] This does not mean that a previous thyroid deficiency existed, but rather suggests that there has been no need for the manufacture of thyroid hormone during the administration of the medication. Consequently, when desiccated thyroid is omitted the gland may require some time

to recover and there may be a relative and temporary thyroid deficiency in normal children who had taken thyroid for suspected cretinism. This situation will correct itself, but if a true thyroid deficiency existed previously, the characteristics of such will gradually develop. Some individuals slow down fairly rapidly on discontinuing thyroid while others take a much greater time to develop these signs and symptoms. It is doubtful if great harm can be caused by attempting to establish the diagnosis definitely by this means. The procedure is to be recommended in childhood, but probably should be dis-

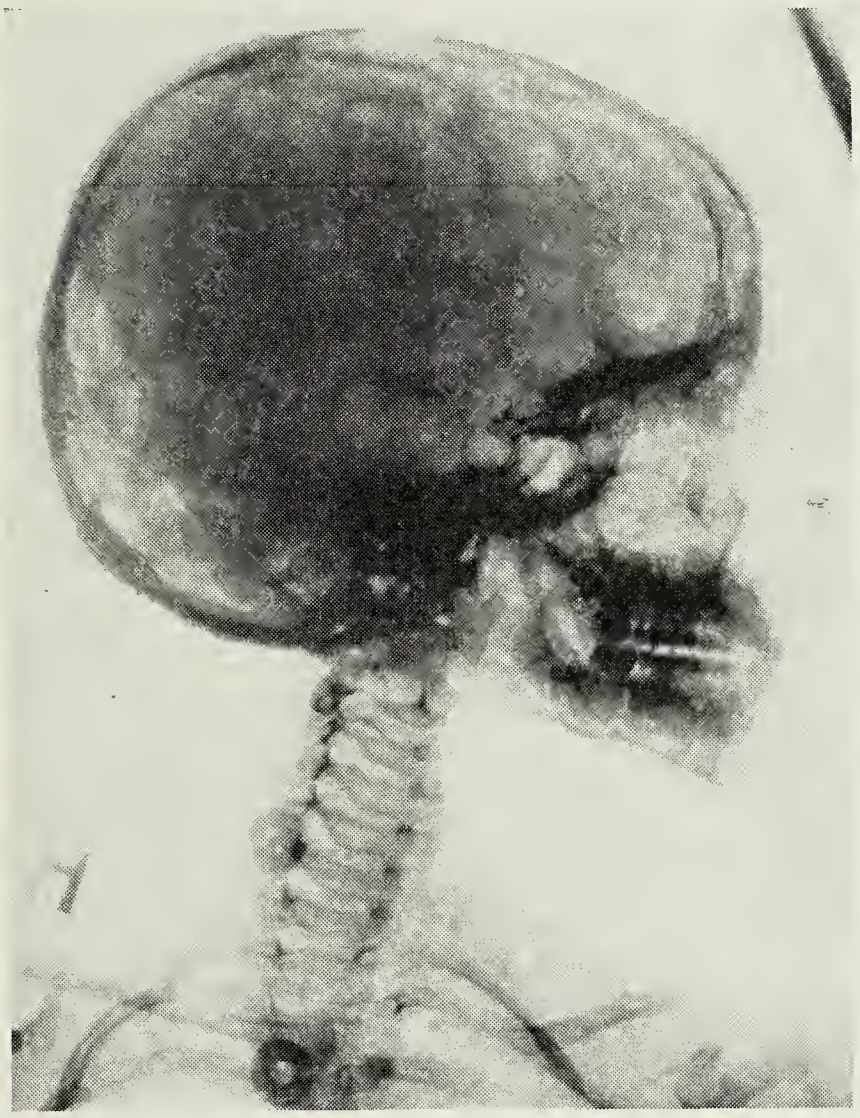


Fig. 36.—Skull of a cretin showing an enlarged sella. Sella measures 11 mm. deep and 11 mm. anteroposteriorly. Average normal measurements for this age (11 years) are 9.36 by 6.18 mm. (From: Hurxthal, L. M. and Musulin, N.: Cretinism. Am. J. Med., *1*:70 [July] 1947.)

couraged in infancy since time is so valuable in the prevention of irreversible changes of thyroid deficiency in the central nervous system.

Desiccated thyroid may be given with little danger in childhood. The vascular system is more elastic and it is unlikely that any serious damage can ensue. A dose of 0.065 gm. (1 grain) per day should be adequate from the ages of 4 to 8 or 9, and after that it should be increased to 0.12 gm. (2 grains) by the age of 18. It is probably better to give a little too much than not enough. It has been reported that some cretins[6, 43] do not respond with the usual acceleration of growth seen so commonly. The administration of methyl testosterone in doses

of 10 to 20 mg. a day along with desiccated thyroid has been shown to increase growth.[43] Its effect, however, is transient and the long-range results have yet to be evaluated. It is well to avoid undue irritability and nervousness by suddenly flooding the system with desiccated thyroid, although it is probably not harmful to begin with the maintenance dose in children. One can give one-quarter to one-half of the optimum dose for a period of several weeks to a month to avoid too rapid a change.

If cretinism is present with a large adenomatous type of goiter a striking decrease in size may follow the administration of thyroid. It is assumed, and I believe it has been demonstrated, that hyperplasia is present in such goiters even though myxedema exists. This suggests the effect of excess thyrotrophic hormone in attempting to cause adequate production of thyroid hormone but the thyroid gland is incapable of rapidly doing so. This inability may be the result of some goitrogenic agent so far unknown or of an inadequate supply of iodine. Eventually the thyroid may respond to stimulation and produce thyroid hormone, thus tending to relieve the patient of myxedema.

The administration of iodine in such instances, as a rule, has no effect. Lerman[25] reported one instance of a cretin with goiter in whom the administration of iodine caused a rise in metabolic rate. Subsequent observations were not made but the experiment suggests that with therapeutic doses of iodine the thyroid could manufacture its hormone.

We have observed a child who apparently had a medium-sized colloid goiter and to whom iodine had been given. Severe myxedema developed and was relieved when iodine was discontinued. It can be postulated in this case that part of the thyroid was relatively inactive. Within the colloid goiter there were comparatively few follicles with hyperplasia which were working hard, but successfully, to maintain a normal output of thyroid hormone. In such a case, iodine could cause involution and a reduction of thyroid hormone output by these follicles.

Cretins with large goiters should not be subjected to surgery until adequate treatment of thyroid deficiency has been carried out. Should tracheal compression or intrathoracic extension persist, operation is advisable. Their removal for cosmetic purposes is always justified. Biopsies should be made more frequently for investigative purposes.

PROGNOSIS

Of thirty-five cases studied by the author, eighteen were followed through to maturity, and only three cases were considered to be of normal intelligence (Fig. 28). Only one was an idiot (Fig. 33), while the rest had sufficient intelligence to be employed at menial tasks and earn their own living. None of the individuals attained a normal height age, but in a few instances the height was such that it could have been within normal limits. Early treatment had been neglected in many, chiefly because the condition had not been recognized. It is thought

that the end results would have been better had treatment been started earlier in the course of the disorder.

Acceleration of and maintenance of normal growth rate with adequate treatment is the rule. It is seldom more rapid than would be expected for the estimated height age. Larger doses of thyroid than optimal might have increased growth rate beyond normal in some of our cases had it been given. The wisdom of this procedure, however, is doubtful since bone maturation takes place at an accelerated rate, so that eventually the attained height at maturity would probably be no greater because of epiphyseal closure than if a normal rate of growth had been maintained. It was concluded that the height lost and mental deterioration during the period of thyroid deficiency cannot be regained but may advance normally from the time of treatment. Mental age is to be distinguished from mental apathy, the latter vanishing with treatment. Nervous system disorders, such as stuttering, speech defects, or occasional tremor or spasticity are rarely overcome. Hearing, however, may be improved. In this country deafness appears to be uncommon among cretins but is more frequent in adult myxedema.

Normal sexual development and fertility can be expected with adequate treatment (Fig. 31). European literature[9, 14] indicates that untreated cretins can propagate successfully. It would seem that such cases are examples of recovery of thyroid function permitting adequate development of spermatogenesis and ovulation.

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ENDOCRINE PROBLEMS DURING ADOLESCENCE

Willard O. Thompson, M.D., F.A.C.P.*

The signs, symptoms and frequency of endocrine disorders vary somewhat at different ages. During adolescence, important changes occur in the development of the skeleton, musculature and secondary sex characteristics and the integrity of all glands of internal secretion is essential for these changes. If hypogonadism is present throughout puberty it produces irreversible changes in the skeleton. Normal function of the pituitary and the thyroid is essential for normal growth in height.

It will be the object of this clinic to discuss the more important endocrinopathies that occur during adolescence.

THE ANTERIOR LOBE OF THE PITUITARY

During adolescence, glandular disturbances resulting from both hypopituitarism and hyperpituitarism are encountered.

HYPOPITUITARISM

Deficiencies of all functions of the anterior lobe of the pituitary may be encountered during adolescence. The most common ones are those associated with deficiencies of the growth and gonadotropic factors. Deficiencies of both factors may occur in the same individual or there may be a deficiency of one, with normal production of the other.

Complete Absence of Function (Panhypopituitarism).—In rare instances, notably as the result of a chromophobe adenoma or a suprasellar cyst, all of the functions of the anterior lobe of the pituitary may be lost with the result that growth is greatly retarded, sexual development fails to occur and there is a marked deficiency of adrenal cortical function producing lowering of the blood pressure and sometimes reduction in the concentration of sodium in body fluids. The disturbance in growth and development is very great. Individuals with such a pronounced pituitary deficiency are usually rather thin and appear older than they actually are. A marked pituitary deficiency may, of course, occur without a tumor being present. If a tumor is present which compresses the optic chiasm, it must be removed surgically.

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Patients with a complete pituitary deficiency have a low resistance to surgical procedures, and should undergo glandular therapy before operative interference is undertaken.

There are no very satisfactory pituitary extracts at the present time. Treatment of this extreme form of hypopituitarism therefore involves the treatment of the various deficiencies that result from the hypopituitarism. Specifically, the hypothyroidism, hypogonadism and hypoadrenalism should be corrected by appropriate measures and then operative removal of the tumor undertaken if indicated. Following surgical intervention, a permanent pituitary deficiency remains and the glandular therapy instituted before operation must be continued.

Two developments have recently occurred in Evans' laboratory which may result in some improvement in therapy in patients of this type. One is the isolation of a purified growth hormone, and the other, the isolation of the adrenocorticotropic hormone which stimulates some of the functions of the adrenal cortex.

Pituitary Dwarfism.—Pituitary dwarfism may be part of the picture of so-called panhypopituitarism. It may be present without impairment of other pituitary functions, or there may be a partial loss of other functions, such as the gonadotropic and thyrotropic functions. Pituitary dwarfism usually begins during the first few years of life. Most pituitary dwarfs have relatively normal body proportions up to the age of puberty. The most outstanding abnormality is their short stature. At the age of puberty, if there is an associated hypogonadism, the effects of this disorder on the skeleton become evident.

Unfortunately, there is at the present time no commercial preparation of the pituitary growth factor that is very effective. If there is an associated hypogonadism at least part of the skeletal and muscular growth associated with normal puberty can be produced in the male by the administration of chorionic gonadotropin and male sex hormone. In the female the administration of estrogenic material causes a corresponding type of growth. These materials, however, are not substitutes for the pituitary growth hormone without which the skeleton cannot become normal in length. They induce that component of growth associated with puberty. If there is no associated hypogonadism, puberal growth will occur without the administration of these materials.

There is no way at the present time of causing normal growth in height of the pituitary dwarf regardless of the age at which treatment is started. The use of desiccated thyroid is of no value in stimulating growth in these individuals. While both the thyroid hormone and pituitary growth hormone cause growth of the skeleton in length, one is not a substitute for the other and the skeleton cannot attain normal length if either is absent.

Fröhlich Syndrome.—The Fröhlich syndrome is characterized by fullness of the breasts and abdomen, small genitalia, genu valgum,

narrow shoulders and broad hips. In the more extensive forms, the abdomen is very large and hangs down like an apron over a lower transverse fold which lies just above the pubic bone. This abnormality occurs in both sexes and usually begins between the fifth and tenth year of life but it may appear at any age before puberty. Patients who suffer from this disorder are usually normal in height. The sella turcica is often smaller than normal, although in very rare instances, a tumor may be present. There is sometimes a moderate lowering of the basal metabolism. The rate is rarely lower than minus 25 per cent. It is generally considered that the hypothyroidism and the hypogonadism are the result of hypopituitarism.

The most important part of the treatment in the male is the administration of chorionic gonadotropin which stimulates the production of male sex hormone by the interstitial cells of the testes. As a result of this therapy alone, normal configuration of the skeleton is assured. The hypothyroidism should be corrected by the administration of desiccated thyroid, and the obesity, by a suitable weight reducing diet.

In the female, chorionic gonadotropin is not as effective a therapeutic agent as in the male, and it is usually better to rely on substitution therapy with estrogenic material.

Secondary Eunuchoidism.—Eunuchoidism may be secondary to lack of stimulation of the gonads by the pituitary. Eunuchoid individuals are usually normal in height. In the male, eunuchoidism may or may not be associated with undescended testes.

Diagnosis of this type of eunuchoidism can be made chemically by determining the production of gonadotropic hormone in the urine. If this is present in normal quantities or in excess, it may be assumed that the eunuchoidism is primary in type. If it is present in reduced quantities, it may be assumed that it is of the secondary type.

If laboratory facilities for hormone assays are not available, the diagnosis can be made in the male by a therapeutic trial of chorionic gonadotropin. If this material induces growth of the genitalia and the development of other secondary sex characteristics, it may be assumed that the eunuchoidism is of the secondary type.

In the female, stimulating agents are not very satisfactory and it is usually best to use some suitable estrogenic material. Since the deficiency is permanent, treatment is necessary throughout the patient's life. It is very important to begin treatment at the beginning of puberty so that the skeletal abnormalities associated with hypogonadism will not occur.

Anorexia Nervosa.—Anorexia nervosa may be confused with marked hypopituitarism. It is much more common in the female than in the male and usually begins before the thirtieth year of life and commonly during the adolescent period.

The underlying cause is usually psychogenic in nature and very often

involves a desire on the part of young women to avoid becoming obese. They usually go on diets of their own choice which are inadequate in many respects. As times goes on, their appetites fail and a marked state of malutrition sets in.

As a result of the malnutrition, various glandular deficiencies develop. There is usually failure of the anterior lobe of the pituitary, and secondary to this, hypothyroidism, hypogonadism and hypoadrenalism. The patients become listless and the basal metabolism may drop to a level of minus 40 to minus 45 per cent. The external genitalia show some atrophy. The breasts lose fatty tissue but usually remain fairly well developed and contain a considerable amount of breast tissue. The blood pressure drops because of the deficiency of the adrenal cortex.

Various emotional factors of a religious and sexual nature may be involved.

A great deal of improvement may be produced by increasing the caloric intake, but it is extremely difficult to persuade patients of this type to eat an adequate amount of food. However, correction of the nutritional state alone does not cure the patient. The glandular deficiencies produced by the state of malnutrition may persist for several years after the body weight reaches a normal level.

Inasmuch as satisfactory pituitary extracts are not now available, the glandular deficiencies secondary to the hypopituitarism must be corrected. Thus, the patients must receive desiccated thyroid, estrogenic material and adrenal cortex extract. It is usually necessary to continue the administration of these materials for a period of two or three years, after which time some recovery may occur in the patient's own glands of internal secretion as a result of the improved nutritional state. However, the glandular deficiencies may persist to some extent for a period of many years.

It is important in the treatment of these patients to combine adequate glandular therapy with psychotherapy. Striking improvement occurs if the patients follow instructions, but in some instances it is extremely difficult to secure their cooperation and the disease persists for a long period of time.

Some patients go from one extreme to the other and alternately lose excessive amounts of weight and gain excessive amounts of weight. In them the hypothyroidism and hypogonadism which develop during the period of loss of weight may persist when the body weight goes above the normal level.

HYPERPITUITARISM

Gigantism.—Pituitary gigantism is rare and is caused by an overproduction of pituitary growth factor before epiphyseal closure. The condition may be associated with an eosinophilic adenoma of the anterior lobe or with hyperplasia of the eosinophilic cells without an adenoma. Sometimes the development of an eosinophilic adenoma results in pressure on the other cells of the anterior lobe so that their

function is impaired. As a result, some individuals with gigantism suffer from mild degrees of hypothyroidism and hypogonadism.

In the early stages of pituitary gigantism, it is not easy to make a diagnosis if a tumor is not present. In determining whether gigantism is present or not, it is very important to know what the normal height of the individual is. The family history is of great value and it is also of importance to determine the growth expectancy from any suitable growth data, such as a Burgess chart.

Pituitary gigantism is usually treated by roentgen-ray therapy over the pituitary. The pituitary is rarely large enough to compress the optic chiasm. It is only under these circumstances that operative interference is considered. As the time of epiphyseal closure approaches, the facial appearance of the individual gradually becomes acromegalic and gigantism is gradually replaced by acromegaly. The overproduction of growth factor is not easy to correct by roentgen-ray therapy and is apt to persist for many years. If any glandular deficiency is associated with gigantism, it must be corrected by appropriate therapy.

THE THYROID

The most common thyroid disturbances encountered during adolescence are simple goiter, hypothyroidism and hyperthyroidism.

Simple Goiter.—Simple goiter has almost been eliminated by the use of iodized salt. In goitrous areas of the world in which endemic goiter has lasted for generations, endemic cretinism has been the result.

Endemic cretinism has not occurred in the goitrous areas of this country because endemic goiter has not lasted long enough and has now been eliminated. Endemic goiter and endemic cretinism did, however, occur in many domestic animals in goitrous areas and were eliminated by the simple expedient of adding iodine to their intake of food.

The prevention of simple goiter by proper prophylaxis is an important public health measure. One of the end results of simple goiter is the development of adenomas in the thyroid which may give rise to hyperthyroidism and carcinoma.

Hypothyroidism.—Hypothyroidism may develop during adolescence or may be the result of a thyroid deficiency occurring at an earlier age. The manifestations of hypothyroidism developing during adolescence or childhood are similar to those of adult myxedema with the exception that hypothyroidism occurring during the developmental period results in dwarfism, hypogonadism and delay in epiphyseal closure.

The milder forms of hypothyroidism produce less marked changes. There may be some delay in the onset of puberty. Menstruation may be scantier and the menstrual periods may be prolonged. There is often a little dryness of the skin and constipation. Many of the milder forms of hypothyroidism in adolescence are secondary to hypo-

pituitarism and the distinction between primary and secondary hypothyroidism can be made only by the administration of desiccated thyroid. If all of the manifestations of hypothyroidism are corrected in this manner, it may be assumed that the hypothyroidism is primary, whereas if they persist, it may be assumed that the hypothyroidism is secondary in type.

When myxedema develops during childhood, it is extremely important to continue the treatment during the period of adolescence because a normal concentration of thyroid hormone is essential for all of the glandular changes that occur during this period. If the treatment of cretinism (hypothyroidism of infancy) is delayed until the onset of adolescence, growth to normal height will not occur although a great deal of improvement will be produced.

The development of the brain is affected more than that of the skeleton. The brain doubles in size during the first year of life, and absence of the thyroid hormone for only a few months during this period, results in permanent damage to this organ.

The skeleton can withstand a longer period of absence of thyroid hormone and recover almost completely. However, if the treatment of cretinism is delayed until the onset of adolescence, the skeleton can never become normal in length, although it may grow a great deal.

Hyperthyroidism.—Hyperthyroidism is not as common during alolescence as it is a little later in life. It is usually of the exophthalmic goiter variety, and nodular goiter with hyperthyroidism is not very often encountered. Manifestations of the disease are the same as in later life and the treatment is the same.

There has been a reluctance on the part of some workers to remove any thyroid tissue in patients with hyperthyroidism during the period of adolescence, but there is no reason to alter the treatment at this age.

Important advances have occurred in the treatment of toxic goiter in the last few years, notably as the result of the introduction of antithyroid drugs and radioactive iodine. Radioactive iodine is still undergoing therapeutic trial.

The value of antithyroid drugs has been definitely established. Propylthiouracil is the one most commonly used. It produces fewer toxic reactions than thiouracil although it is not completely free from danger. The possibility of the development of agranulocytosis, although rare, must always be borne in mind. This drug has been used in two ways: (1) to treat the disease medically, (2) to prepare patients for operation. It has been demonstrated that, when used for medical management, a permanent remission occurs in more than half of the patients if the basal metabolism is maintained at the normal level by the administration of the drug for at least one year before it is discontinued. In unsuccessful cases, a permanent cure may result with a second or a third course of treatment.

When propylthiouracil is used for preoperative preparation, it

possesses the great advantage over iodine that it completely abolishes the hyperthyroidism so that patients come to operation with a normal rate of basal metabolism. As a result, the mortality from thyroidectomy has dropped almost to the vanishing point. The usual procedure is to give propylthiouracil until the basal metabolism becomes normal and then give iodine in addition for one week preceding operation. Propylthiouracil may be omitted at the time of operation but the administration of iodine is continued until the patient is discharged from the hospital.

While the development of antithyroid drugs represents an important advance, no drug available at present represents the final answer to the problem. It is desirable to have a drug which will control thyrotoxicosis permanently without producing any toxic symptoms. Moreover, there is enough evidence available at the present time to indicate that exophthalmic goiter is not a simple disease but is the result of a complicated chain of events in which the thyroid is only one link. The cause of the disease probably lies outside of the thyroid gland and involves stimulation of the thyroid by the pituitary. The time may therefore come when the treatment of this disease will not be directed at the thyroid at all, but at the mechanism involved in thyroid stimulation. The treatment of hyperthyroidism is in a state of flux and everything written on the subject up to two or three years ago is now out of date.

THE PARATHYROIDS

Diseases of the parathyroids are only occasionally encountered during adolescence. Hyperparathyroidism is very rare at this age, but parathyroid tetany is occasionally encountered. It may be of the spontaneous or of the postoperative variety. The manifestations of hypoparathyroidism are the same in adolescence as in later life and the disorder can be completely relieved by appropriate treatment with calcium and dihydrotachysterol or large doses of vitamin D. It is important to make the diagnosis as early as possible so that the development of complications, notably bilateral cataracts, can be avoided. Occasionally, the same patient has hypoparathyroidism and idiopathic epilepsy. Under these circumstances, it is not always easy to determine when epileptic seizures are the result of the parathyroid deficiency and when they are caused by the epilepsy per se. Moderate lowering of the concentration of calcium ions in body fluids appears to predispose to epileptic seizures and individuals with epilepsy may develop epileptiform seizures with only moderate depression of the serum calcium.

THE ADRENALS

Disorders of the adrenals are relatively uncommon during adolescence but are occasionally encountered. In rare instances, Addison's disease develops during childhood. The manifestations of the disease are the same as in later life and the treatment is the same.

Pheochromocytoma (tumor of the adrenal medulla) occasionally develops during the adolescent period with all of the manifestations of over-production of adrenalin including transient attacks of hypertension.

Masculinizing tumors of the adrenal cortex are occasionally encountered in females during the period of adolescence with overproduction of androgenic material and the development of hirsutism, lowering of the pitch of the voice, masculine musculature and enlargement of the clitoris. Treatment consists of the removal of the tumor unless it is malignant and bound down to surrounding tissues so that it is inoperable.

THE TESTES

Theoretically, both hypogonadism and hypergonadism, may be encountered but in actual practice hypergonadism is rarely seen. Cases of hypogonadism constitute an important part of the endocrinopathies encountered during adolescence. Hypogonadism may be primary or secondary. The primary type is the result of a defect in the testis itself, and the secondary type is caused by lack of stimulation of the testis by the anterior lobe of the pituitary.

The testis contains two important functioning units, the seminiferous tubules and the interstitial cells of Leydig. There appears to be a reciprocal relation between these two parts of the testis, and as a rule, in hypogonadism there is a deficiency of both functions. However, they may be affected independently of one another so that azoospermia may be present in an individual who produces fairly large quantities of male sex hormone. Conversely, spermatozoa may be produced in the presence of deficiency quantities of male sex hormone. In actual practice, this phenomenon is rarely encountered. Defective spermatogenesis with fairly adequate production of male sex hormone is more common.

The anterior lobe of the pituitary produces two gonadotropic hormones. One is follicle-stimulating, and the other is luteinizing. A deficiency of one is usually associated with a deficiency of the other, but they also may vary independently of one another so that there may be an adequate quantity of follicle-stimulating hormone and a deficient quantity of luteinizing hormone, or the reverse. Thus, primary and secondary hypogonadism must be further subdivided into primary and secondary types involving a deficiency of both testicular functions, and primary and secondary types involving a deficiency of either the spermatogenic function or the androgenic function without disturbance of the other. Theoretically, then, there are at least six different types of hypofunction of the testes.

In actual practice, an individual showing a deficiency of one function usually shows some evidence of deficiency of the other, although one type of deficiency may predominate. A great deal of information is now being accumulated on various types of testicular hypofunction by the combined use of hormone assays and testicular biopsy.

Primary Hypogonadism.—The most common type of primary hypogonadism encountered during adolescence is *eunuchoidism.* In this condition, there is loss of testicular function of varying degrees and it may be associated with intra-abdominal undescended testes or with small atrophic testes in the scrotum.

As stated in the section on the pituitary, the type of hypogonadism may be determined either by measurement of the gonadotropic hormone in the urine or by a therapeutic trial of stimulation therapy using chorionic gonadotropin. It is important to begin treatment early in puberty so that the skeletal abnormalities caused by hypogonadism will not occur. When hypogonadism persists during puberty, the trunk remains short in proportion to the extremities, the shoulders are narrow and the hips broad. Genu valgum is usually present. All of these abnormalities are prevented if adequate treatment is started early in puberty. Genital growth can become maximum only when adequate treatment is started at the age of 11 or 12 years. If treatment is delayed until after the age of puberty, genital growth will occur, but it does not become maximum.

Stimulation therapy is not entirely satisfactory at the present time. The only effective stimulating agent, namely, chorionic gonadotropin, is luteinizing in character and therefore stimulates only the function of the interstitial cells and not that of the seminiferous tubules. Other gonadotropic hormone preparations available at the present time, namely, pituitary gonadotropin and equine gonadotropin, contain a preponderance of follicle-stimulating material but cause only transient or inadequate stimulation of the seminiferous tubules.

Treatment with chorionic gonadotropin should be carried out first to determine whether or not any response occurs. If there is no response within a few weeks, it should be discontinued and treatment with testosterone propionate begun. This should be administered in a dose of 25 mg. three times a week by intramuscular injection. Since the deficiency is permanent, treatment must be continued for the rest of the patient's life.

Eunuchism is rare during adolescence although patients are occasionally encountered in whom testes have been lost as a result of injury or have been completely destroyed by infection. The treatment is the same as in the primary type of eunuchoidism and involves the administration of testosterone propionate.

Secondary Hypogonadism.—The most common type of secondary hypogonadism associated with puberty is that encountered in the Fröhlich syndrome. Secondary types of eunuchoidism are not uncommon with or without undescended testes. Chromophobe adenomas of the pituitary are rare but are occasionally encountered during adolescence, and when present, always result in a secondary type of hypogonadism. As already indicated, the presence or absence of secondary hypogonadism can be determined by the clinical response of the patient to chorionic gonadotropin.

Undescended Testes.—Failure of testicular descent may be either unilateral or bilateral, and when bilateral, may be associated with eunuchoidism. Undescended testes should be treated at a very early age, but cases are often encountered during puberty in which treatment has not been carried out. If puberty has already started and some genital growth has occurred without testicular descent, then operative correction of the abnormality should be undertaken without glandular therapy. If the patient is seen at the beginning of puberty before any genital growth has occurred, treatment should be carried out with chorionic gonadotropin. A dose of 500 international units should be administered three times a week by intramuscular injection for from eight to ten weeks. If descent fails to occur after moderate genital growth has taken place, the testes should be brought into the scrotum by operation. It is important that the operation be carried out by a surgeon who has had a great deal of experience in the correction of this abnormality. There are many delicate structures in the spermatic cord, including the artery that supplies the blood to the testis. When an undescended testis is brought down into the scrotum at puberty, it usually enlarges, but it remains smaller than the testis that has been in the scrotum from the time of birth. Glandular therapy is effective in correcting the deficiency in only about 25 per cent of the cases of undescended testes but is valuable treatment preceding operation because of the enlargement it produces in all of the parts involved. This enlargement makes operative correction of the abnormality much easier.

Tumors of the Testes.—Tumors of the testes are rare during adolescence although feminizing tumors and various types of malignant tumors do occur.

THE OVARIES

Hypofunction of the ovaries is common but clear-cut cases of hyperfunction are difficult to demonstrate. As in the case of the testes, hypofunction of the ovaries may be either primary or secondary. Pituitary, equine and chorionic gonadotropins are not very effective in the female. They do produce some stimulation of function. In some young women with secondary amenorrhea, menstruation has been produced with pituitary gonadotropin. Its effect, however, appears to be temporary. Chorionic gonadotropin in large doses (8,000–10,000 units daily) may produce cysts of the ovaries. In some women with secondary hypogonadism it may produce moderate stimulation of ovarian function in moderate doses such as 500 I.U. three times a week. In most cases of hypogonadism in the female, it is necessary to resort to substitution therapy. Early diagnosis is important but much more difficult in the female than in the male because of the greater difficulty in palpating the gonads. Treatment is therefore apt to be started at a later age than in the male with the result that the skeleton is likely to be permanently damaged.

The manifestations of hypogonadism in the female are similar to those in the male including the lack of development of the secondary sex characteristics and the changes in the skeleton.

The most common type of secondary hypogonadism is that associated with the Fröhlich syndrome. In rare instances, as in the male, it may be associated with a chromophobe adenoma of the pituitary or with a suprasellar cyst. In most cases of hypogonadism in the female, it is necessary to rely on substitution therapy with estrogenic material.

ABNORMALITIES OF DEVELOPMENT

Various abnormalities of development may be encountered in both the male and the female during the adolescent period. Some defect may occur in the development of any part of the genital apparatus. One of the most common developmental defects is pseudohermaphroditism in which the individual has the external organs of one sex and the internal organs of the other. Very often genetic males are brought up as females because of the appearance of their external genitalia. There may be a vaginal opening with the urethral opening in the feminine area. The urethral folds fail to unite with the result that hypospadias develops. Testes may be palpable in the inguinal region on either side although they may be inside the abdomen. At puberty, the clitoris enlarges to the size of a small penis. The voice changes, hair appears all over the body and a masculine type of musculature develops. Individuals of this type are commonly brought up as females and the mistake is discovered only after they have gone through puberty. Careful palpation fails to reveal any uterus. The upper two-thirds of the vagina may be absent, but the lower vagina which comes from a different source embryologically, is present.

I recently observed an interesting and distressing abnormality of development in a young woman 18 years old. She consulted me because of her failure to menstruate. It was the mother's impression that she had an ovarian deficiency. Careful examination of the patient revealed the fact that most of her secondary sex characteristics were well developed. Her breasts, although not large, were within normal limits of size and contained a large amount of breast tissue. Her labia minora were well developed. She had a normal amount of pubic hair. Her body proportions were normal. There was a very small opening in the vaginal area. Examination under an anesthetic showed that this was the urethral opening and that no vaginal opening was present. On repeated rectal examination, no uterus could be felt. Whether a vagina is present or absent is still to be determined by surgical exploration. The adequate development of all of her other secondary sex characteristics leaves no doubt that the patient has normally functioning ovaries. An abnormality of this type is apt to result in very distressing emotional complications.

STATURAL DISTURBANCES IN PEDIATRIC PRACTICE

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Disturbances in linear growth as manifested by understature, undersize or dwarfism (real or supposed), or by overgrowth, oversize or gigantism are important causes for seeking medical advice. We have studied a number of boys and girls of abnormal stature, the majority of whom have been unusually small. A number of categories have been selected for this clinical presentation.

UNDERSTATURE

Boys and girls exhibiting varying degrees of stunted growth may experience problems in their personality adjustment. They may be retarded in their emotional development as a consequence of being treated as younger than their actual age. They may develop compensatory types of behavior which may take the form of minor delinquencies, an excessive degree of self-assurance or a submissive attitude and an attempt to play an infantile role. The physician can play an important role in the management of patients with understature and help them make a satisfactory adjustment so that they can attain a normal emotional and social development.

The doctor must have full appreciation of the many causes for arrested skeletal development and the multiplicity of factors encountered which contribute to the picture of the undersized patient. The physician must realize that some children exhibiting undersize may spontaneously improve during adolescence. It is to be emphasized that some alterations must be made in our accepted standards as to when growth stops, for we now know that growth continues in numbers of patients past the usual accepted periods. By roentgenologic studies of the long bones we can determine the question of continued linear growth.

There are some undersized children in whom the condition apparently is not genetic and is unrelated to disturbances of the endocrine, skeletal, renal, cardiovascular and other systems of the body. Talbot recently studied such a group in whom the stunting of growth was seemingly caused by caloric deficiency due to feeding difficulties as-

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sociated with various maladjustments. It has been suggested that when children are constantly on small dietary intakes there is a tendency for an adaptation on the part of the pituitary to provide for slower growth. We have noticed that some infants with feeding difficulties fail to grow at a normal rate, nevertheless dietary inadequacies seem to play little part in our dwarfish patients usually seen at a later age period. In other infants growth proceeded at a normal rate until the onset of an infectious process with a resultant persistent anorexia. After recovery from the illness growth seemed to proceed at a retarded rate. The fact that an increased caloric and protein intake does not always stimulate growth in these individuals emphasizes that presumably development proceeds at a normal rate only in the presence of adequate anabolic hormones. It has been suggested that spurts in growth may be accomplished by the daily administration of oral androgens at regular intervals.

Hypothyroidism.—Of the endocrine causes for dwarfism, thyroid deficiency is the most readily recognized, the following aiding the diagnosis: lowered basal metabolism, elevated cholesterol, diminished or absent urinary creatine excretion, decrease of serum protein-bound iodine, retardation of carpal development, epiphyseal dysgenesis, and spectacular improvement following therapy. We should like to call attention to the little appreciated finding of muscular hypertrophy in association with thyroid deficiency.

It is extremely important to rule out statural underdevelopment due to hypothyroidism in the adolescent. We have had a number of recent experiences which stress this. Failure to make the correct diagnosis has resulted in the loss of valuable time for these children mistakenly treated with growth hormones for years without results.

In 1941 we discussed a patient who was inadequately treated with thyroid extract, who received large amounts of pituitary growth material with no increase in stature. In addition, this patient had constipation, a protuberant abdomen and megacolon. These symptoms led to a diagnosis of Hirschsprung's disease and a subsequent unwarranted lumbar sympathectomy.

The most recent experience is with a 12 year old girl referred because of "lacking in normal physical development, and dryness of skin, suggestive of senility. Anterior growth hormones, vitamins and tonics were administered." Our impression from a cursory examination was that of thyroid deficiency. Several attempts to perform basal metabolic tests were unsuccessful because of lack of cooperation. Peripheral blood studies revealed a hypochromic anemia. The serum cholesterol was 344 mg. per 100 cc. of blood. Electrocardiographic tracings showed T_3 practically isoelectric. There was retardation in ossification of the carpal bones and irregularities of both humeral epiphyses.

Recently a 16 year old high school boy came himself because of undersize and overweight. In our experience it is rare that studies of

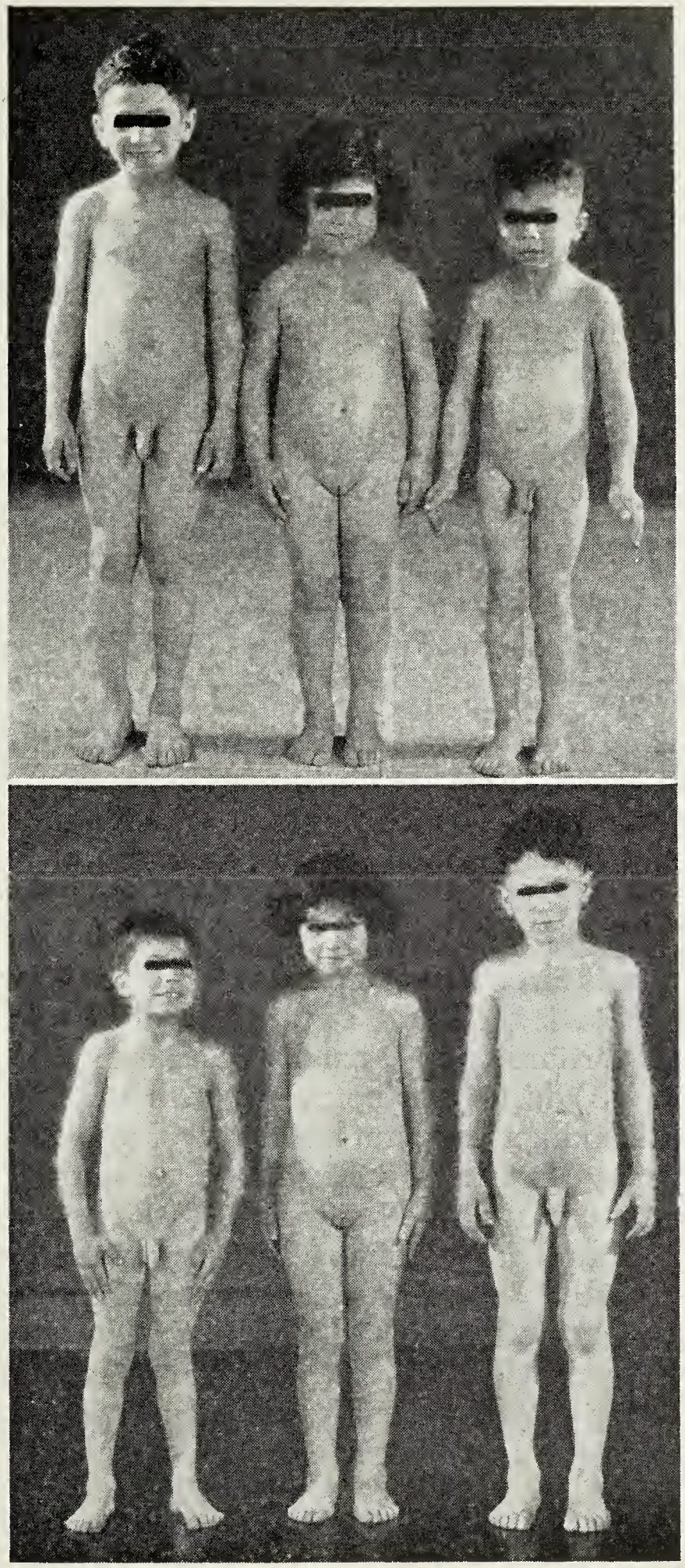

Fig. 37.—*Upper,* Female hypothyroid, aged 8, with brothers of 4 and 6. Came in primarily as a statural problem. *Lower,* Ten months later after receiving thyroid extract.

basal metabolism are not made in fat children and that thyroid extract is not administered for the adiposity. Unfortunately it was not for, had thyroid been given a remarkable transformation would have been

noted. The rate when determined was minus 39, the serum cholesterol was elevated and changes in the carpal centers were consistent with hypothyroidism. With regard to basal metabolism, we should like to emphasize that although a valuable test it is not specific. Hypometabolism is not necessarily synonymous with hypothyroidism. This is borne out in obese children in whom, on the basis of lowered rates, borderline thyroid deficiency is diagnosed. In a number of studies of the usually encountered adiposity there was little other evidence to postulate such a diagnosis.

In our experience, adequate dosage is determined by physical, osseous and mental growth and by the avoidance of severe toxic symptoms. Since a rigid table of dosage is impracticable we prescribe the following average doses:

Age	Daily Dose of Thyroid
6 months to 1½ years	½ to 1½ grains (0.03 to 0.09 gm.)
1½ to 8 years	1 to 3 grains (0.06 to 0.18 gm.)
8 years to adolescence	1½ to 3 grains (0.09 to 0.18 gm.)

Not infrequently it has been necessary for us to employ much larger doses than mentioned in order to obtain optimal responses.

Pituitary Dwarfism.—The diagnosis of anterior pituitary dwarfism is made with but few exceptions by the exclusion of other causes for arrested development rather than by positive proof. The positive diagnosis of this condition by finding roentgenologic evidence of intra- or extracellar tumors is rare. The diagnosis is therefore a presumptive one based on the following clinical evaluations: (1) understature; (2) symmetrical proportions; (3) sexual infantilism; (4) delayed epiphyseal closure; (5) history of normal growth to about two to three years of age with sudden deceleration in rate of growth thereafter. The undersize is usually apparent by the fifth to the sixth year of age.

The treatment of pituitary dwarfism raises two questions: (1) the most effective method for obtaining linear growth; (2) the time at which therapy should be instituted. The use of preparations of the anterior lobe of the pituitary gland, containing the growth-promoting substance, in children with varying subnormal rates of growth, has met with unsatisfactory results in our experience. The administration of chorionic gonadotropins in male children and gonadal substances in male and female children has been accompanied by partially successful results. Our practice is to initiate treatment with gonadotropins in an attempt to obtain linear growth. If in treatment, usually using 25,000 R.U., suggestive results are not obtained, we resort to substitution therapy with androgens, best given intermittently, to promote spurts of growth. Some clinicians believe that the most effective way of increasing height at the present time is through the use of androgens which act as definite factors affecting the growth mechanism. The use of androgens before the age of 16 years has been questioned. Their early

use may produce some damage by inhibiting the gonads. Promiscuous use of androgens must be cautioned against, although it is doubtful whether small doses used interruptedly have any effect in inducing epiphyseal closure.

One of our patients, recently reported, a white girl, aged 12, presented the cardinal signs of classical anterior hypophyseal deficiency. When first examined she was 46 inches tall and weighed 44 pounds, approximately 11 inches and 37 pounds below the average for her age. When she was 15 years old there were no

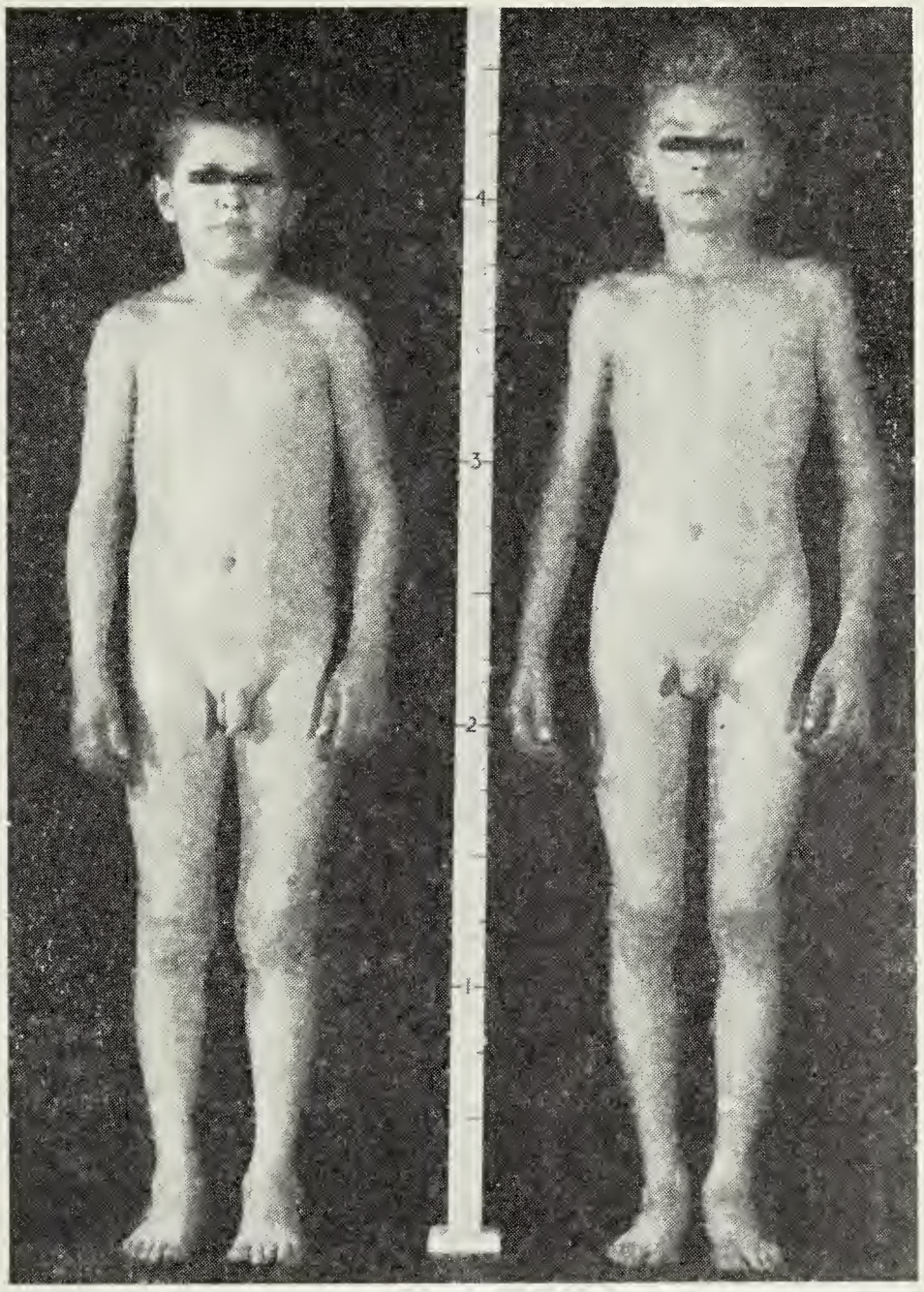

Fig. 38.—Understatured boys, aged 15, before therapy. Excellent growth with the use of chorionic gonadotropins.

secondary sex characteristics and the external genitalia were infantile although structurally complete. Hormonal studies did not reveal any assayable estrogens or gonadotropins. At 17 years of age there was an increase in the rate of growth and at 22 years of age she had attained a low normal height. In 1944, when last seen at the age of 22 years, she was engaged to be married and since has given birth to a normal infant.

This patient illustrates progress without therapy, and the question arises whether some of our dwarfish children are not instances of remarkably delayed puberty.

Ovarian Agenesis.—This is a syndrome occurring in adolescent girls characterized by dwarfism and genital retardation in whom pubic or axillary hair or both may be present (Fig. 39). In addition other defects have been noted, as coarctation of the aorta, osteoporosis and dyschondroplastic changes of the bone, webbing of the neck, and mental retardation.

The cause for the understature is at present not definitely known, but there is reason to believe that genetic defects not directly related to

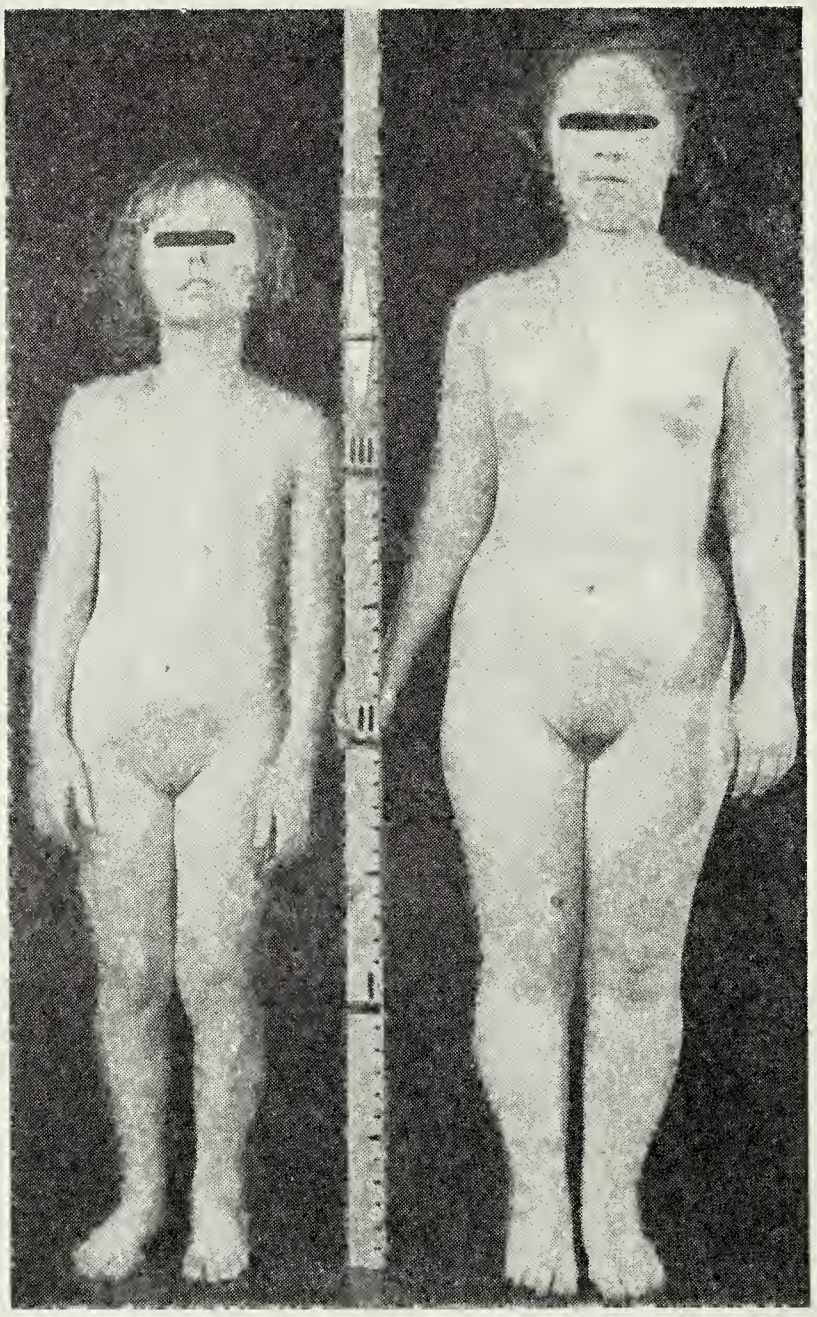

Fig. 39.—Dwarfism with ovarian agenesis (patient aged 17) diagnosed clinically. Pubic and axillary hair not too well demonstrated.

the ovarian agenesis are responsible. Ovarian deficiency due to surgical castration is not accompanied by alteration in growth.

We studied a Negro girl, 16 years of age, who was admitted to the hospital in a moribund state and died a few days later from an unrelated condition. She was readily recognized as a dwarf and because of the pubic hair the diagnosis of ovarian agenesis was suggested. The postmortem examination confirmed this, the essential findings being an absence of ovarian tissue and a hyperplasia of the hypophysis with eosinophilia. There were no abnormalities noted in the other endocrine glands, macro- or microscopically.

Two other girls we studied were given thyroid extract and other available products with little success. Gonadotropic stimulation was tried with little result. Diethylstilbestrol, alone or in combination with progesterone, produced vaginal bleeding and enlargement of the breasts.

Progeria.—Our reason for calling attention to this rare syndrome, characterized by dwarfism, precocious senility, and bony retardation with premature epiphyseal fusion, is to describe a recent experience to emphasize a therapeutic principle.

Our patient had little growth and no weight gain during a period of a year's observation. The use of oral androgens, 20 to 30 mg. daily, brought about a gain of 5 pounds and a growth of 1 inch in one month. Clitoral hypertrophy occurred and treatment was stopped for a period. Weight and growth remained stationary after this with lessening in the enlargement of the clitoris. Reduced dosage of methyl testosterone accomplished continuous development for the period of observation.

Thiouracil to reduce energy output has also been used in the treatment of this condition in which there may be a tendency towards an excessive use of calories.

SKELETAL OVERGROWTH (GIGANTISM)

Abnormally rapid growth in childhood frequently causes concern to parents. In most instances the increased stature is a normal variation, usually being familial or racial. Benign adiposogenital dystrophy of adolescence (Fig. 40) prepuberal hyperpituitarism, the increased statural growth accompanying precocious puberty, and hypogonadism must also be considered. The therapeutic problem in the extremely tall child is to eliminate the presence of a pituitary neoplasm and to avoid possible gigantism.

L. A. is a boy aged 17, height 79½ inches, weight 129 pounds, span 81 inches (Fig. 41). The family history is essentially normal. The patient was referred for treatment with the diagnosis of gigantism possibly due to an acidophilic adenoma. The sexual development is adequate. The visual fields and fundi are normal. The films of the long bones disclose beginning epiphyseal closure about the knees and ankles. At present little can be done since linear growth is practically at an end, epiphyseal closure having stopped the process. Intermittent roentgen ray therapy, chorionic and pituitary gonadotropic hormones, as well as testosterone orally and by pellet implantation, have been used in the treatment of these patients. We have been able, presumably, by the use of androgens, in unusually tall hypogonad males to halt longitudinal growth by causing epiphyseal closure.

Skeletal Overgrowth with Hypergenitalism.—A 7 year old white boy (Fig. 42) exhibited the development of a 12 year old, with marked acne. Studies failed to reveal adrenal, pineal, pituitary or testicular

involvement. It is our opinion that the etiology involves the hypothalamic apparatus. Prior to our observation this boy received roentgen ray therapy to the pituitary. The osseous development reveals marked accentuation of bony growth. If the process continues we intend to employ the therapeutic principle of inhibiting growth by the use of antagonistic hormones, although the possibility of nature herself accomplishing this phenomenon arises. In a previous experience we were

Fig. 40.—Overgrowth in benign adiposogenital dystrophy of adolescence (patient aged 14 years).

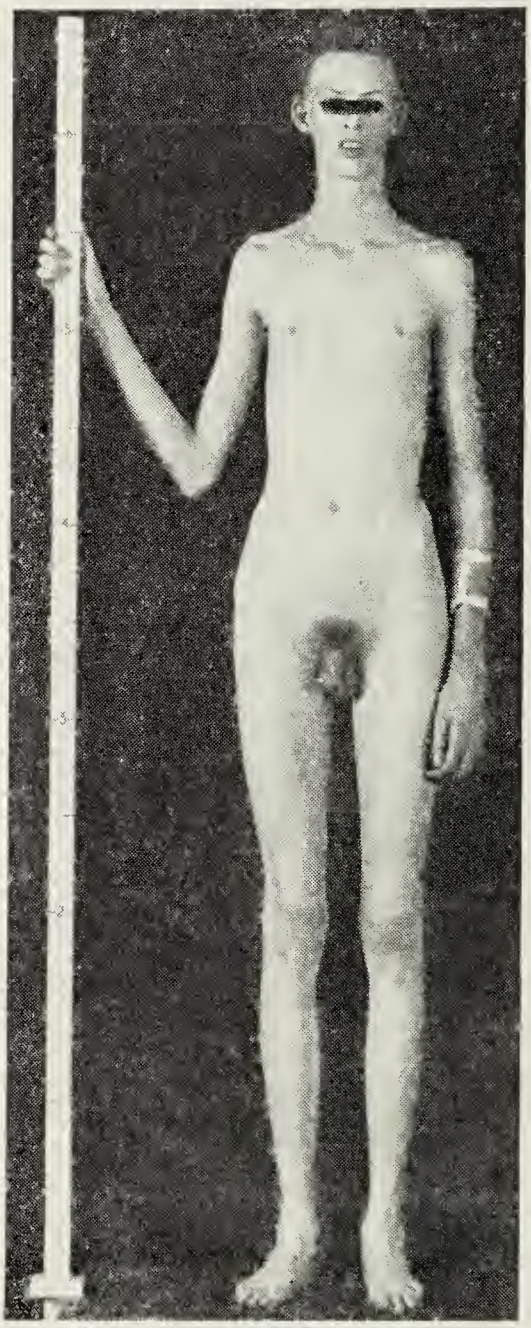

Fig. 41—Extremely tall boy, supposed case of gigantism.

able by the administration of 100,000 units of follicular hormone to cause cessation of both sexual and statural growth. By the use of female sex hormones in the hypersexual male we can accomplish the following: (1) inhibit the gradient of growth; (2) reduce the quantity of androgenic and gonadotropic substances as well as the sexual phenomena; and (3) produce degenerative changes in the seminiferous tubules. The appearance of gynecomastia is a valuable clinical criterion as to the effectiveness of stilbestrol when this drug is employed.

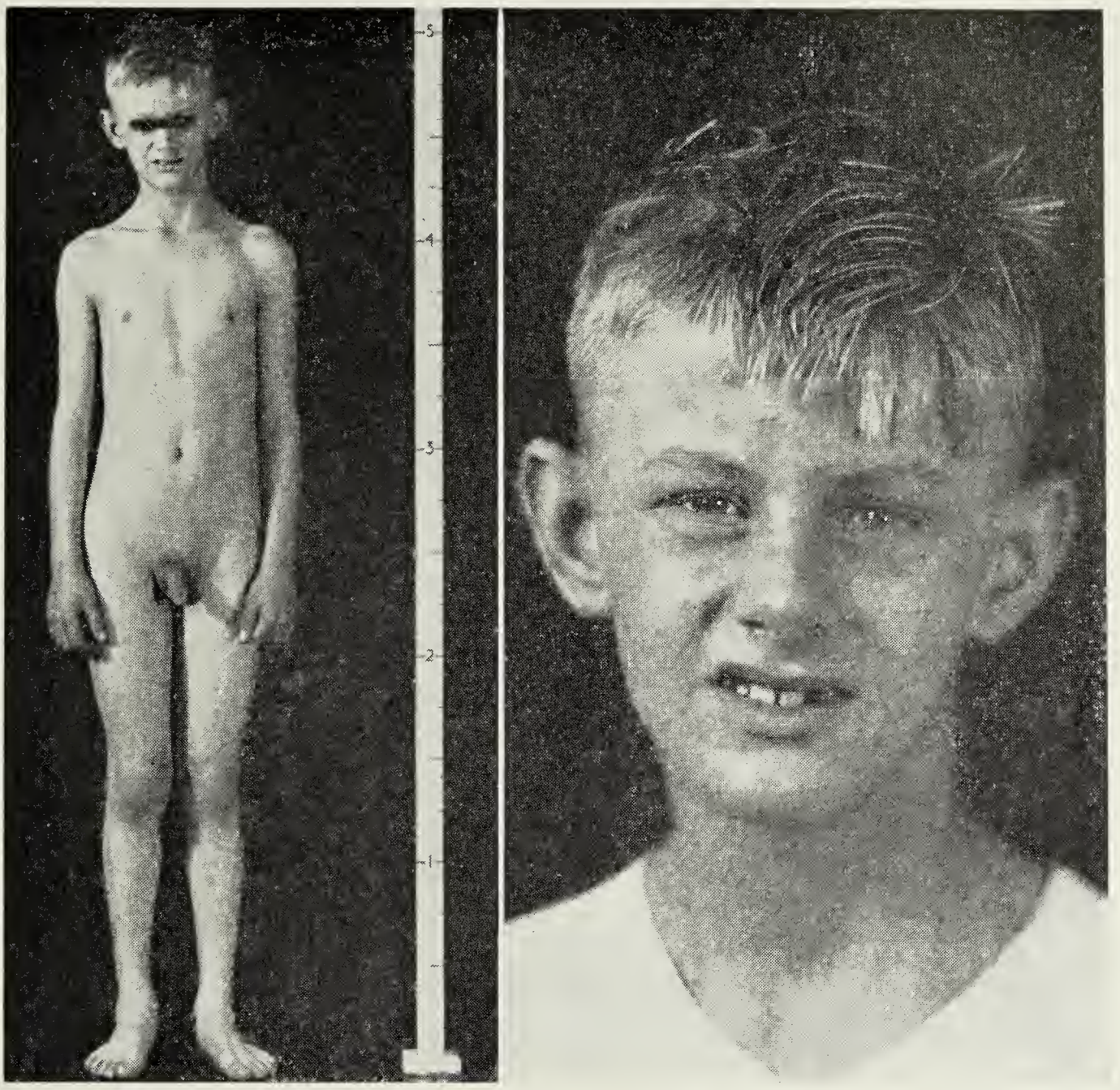

Fig. 42.—Seven year old boy. Skeletal overgrowth with hypergenitalism. *Right,* Close-up of face showing acne.

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CLINICS ON OTHER SUBJECTS

CLINICOPATHOLOGIC CONFERENCES

Cook County Hospital, Chicago

ITALO F. VOLINI, M.D., F.A.C.P.* AND
HANS POPPER, M.D., Ph.D., F.A.C.P.†

CASE I. PERIARTERITIS NODOSA

Clinical History

DR. ITALO F. VOLINI: The first case to be presented today is that of a white man aged 63 who, except for a history of chronic arthritis, was well until the morning of October 29, 1946 when he suddenly developed convulsions. He was admitted to the Cook County Hospital in deep coma and with a blood pressure of 218/118, 4 plus albumin and many granular casts in the urine. The heart was found to be slightly enlarged. Neurologic examination revealed no definite paralysis but the deep reflexes were all hyperactive and pathologic reflexes were present.

Blood examination showed a nonprotein nitrogen of 68 mg. and creatinine of 2.4 mg. per 100 cc. X-ray of the chest showed a thickened left pleura and bronchopneumonia of the right hilar region.

This patient had an "epileptiform" seizure while on the ward, but within two days after his admission there was sudden and dramatic improvement in his condition with complete disappearance of neurologic findings. His urinary and blood chemistry findings also showed improvement. Blood pressure subsided to 178/100, and spinal tap performed twelve days after admission was essentially negative except for a 1 plus Pandy test and 12 cells per cu. mm. The patient was discharged, completely recovered, with a diagnosis of hypertensive encephalopathy.

He was readmitted to the hospital on January 13, 1947 with vague complaints of epigastric and right lower quadrant pain. It was difficult to obtain a coherent and informative history from him because of his

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lethargy and mental stupor. He stated that his epigastric discomfort had started five months prior to admission; the right lower quadrant pain appeared about two months later and was originally accompanied by vomiting. Since the onset of his abdominal symptoms there had been a progressive increase in weakness and in the past two years a weight loss of 50 pounds. There was also a history of frequency and nocturia.

Physical examination at this time revealed an emaciated, lethargic, elderly patient with a temperature of 99° F., respirations 28, blood pressure 196/100. Moist râles were present at both lung bases. The heart was enlarged to the left and showed evidence of auricular fibrillation. Abdominal examination was essentially negative except for slight tenderness and resistance to palpation over the epigastrium and along the course of the ascending colon down to the right lower quadrant. Rectal examination was negative; feces on the gloved finger gave a 2 plus benzidine reaction. The remainder of the physical examination was negative.

Laboratory examination revealed a urine with a specific gravity of 1.028, 4 plus albumin and negative microscopically. The blood contained hemoglobin 58 per cent, red blood cells 3,300,000, white blood cells 19,400 with a differential count of 84 per cent leukocytes, 1 per cent eosinophils, 5 per cent lymphocytes and 5 per cent monocytes.

Before further study could be made the patient's lethargic state rapidly became more marked and he died in coma on January 4, 1947, twenty-two hours after his hospital admission.

The clinical evidence is that of a wasting disease with progressive weakness, hypertension, central nervous system involvement, cardiac hypertrophy with auricular fibrillation, abdominal pain of a vague character and pronounced deviations in the urine and in kidney function. The focalization diagnostically involves the hypertensive state, kidneys and the heart. Malignant hypertension with renal insufficiency and cardiac hypertrophy thus becomes the first consideration. However, the progressive loss of weight and abdominal pain suggest diffuse vascular disease. The rapid terminal course precluded thorough clinical study.

Dr. Hans Popper will now present his findings.

Pathological Studies and Conclusions

Dr. Hans Popper: At autopsy, we saw a rather emaciated body. The heart showed enlargement of both chambers, otherwise no significant changes were noted except for just visible fine nodules around the coronary vessels on the posterior surface. Histologically, we did not see any changes in the vessels themselves, but observed foci of myofibrosis obviously caused by local interference with the blood flow. Gross examination of the lung revealed nothing of significance but, histologically, there were marked changes of the arteries all over the

lung. The media was usually well outlined, often widened, but the muscle fibers could not be made out. Instead, a diffuse fibrinoid degeneration gave the media a homogeneous bright red appearance. Around the vessels there was a wide, densely cellular mantle. Most of the cells were round cells, but polymorphonuclear cells, some of them eosino-

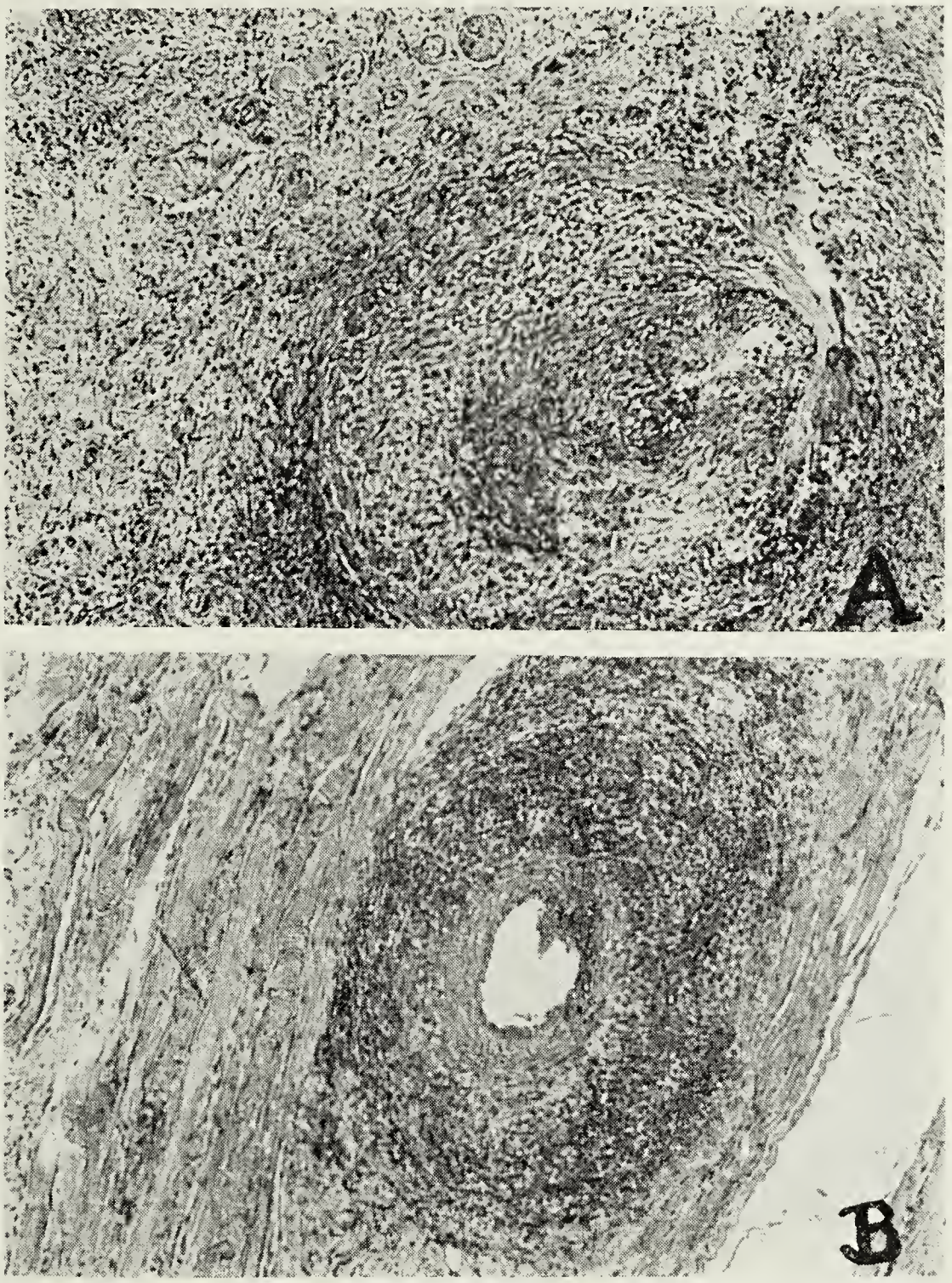

Fig. 43.—*A*, Branch of pulmonary artery revealing occlusion of the lumen by intima proliferation and some thrombosis. The media is widened and reveals a dense cellular infiltration as does the adventitia. *B*, Artery in skeletal muscle. The media is thickened, homogeneous and reveals fibrinoid degeneration. Around it is a wide layer of cellular infiltration.

philic, plasma cells, lymphocytes and a few fibroblasts were also seen. In the media of some arteries there was focal accumulation of polymorphonuclears, similar in many respects to that of an abscess (Fig. 43A). In special stains, the entire media gave marked fibrin reaction, but some fibrin was also found outside the vessels. In other arteries the

media alterations were less conspicuous but the intima revealed fibrotic thickening. Around them there was a loose, moderately cellular granulation tissue containing many fibroblasts and the elastic membranes were almost completely destroyed. This latter picture represents an older stage of the process described before and both together leave no doubt of the diagnosis of *periarteritis nodosa.*

We found similar changes in other organs. Many smaller and larger arteries in the submucosa of the gastrointestinal tract and mesentery were involved; the mucosa itself failed to show alterations. In the pancreas the arteries presented older changes; the vessels in the fatty

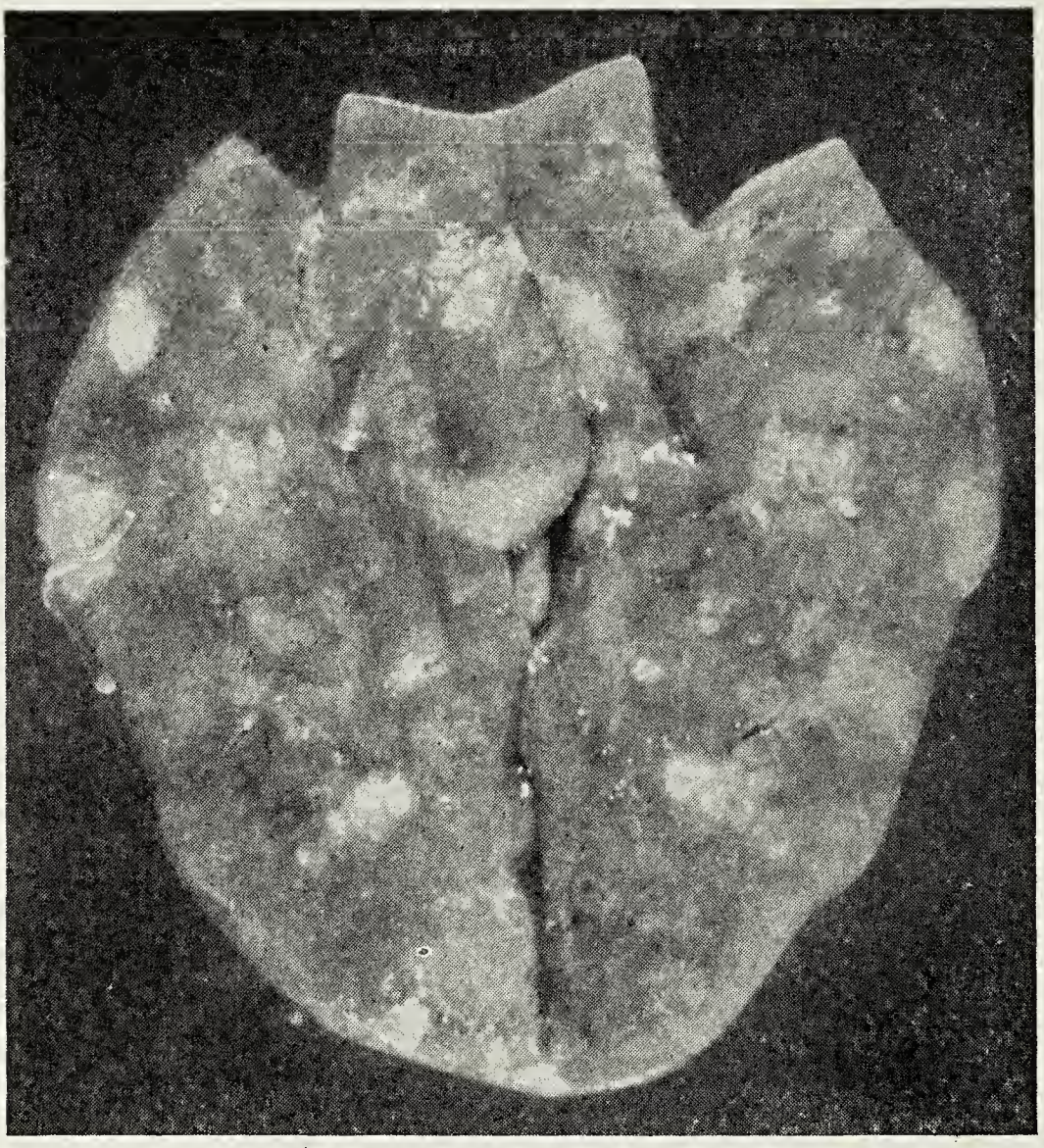

Fig. 44.—Cut surface of kidney revealing larger and smaller infarcts of different age.

capsule of the adrenal showed marked intima proliferation and granuloma formation. The described picture was also presented by many arteries supplying nerves which is so characteristic of diffuse periarteritis nodosa.

The kidneys showed the typical alteration of this disease: many infarcts, some small and some subcapsular; others extending deep into the parenchyma. Most of them were yellow in color, prominent, others were white and sunken (Fig. 44). Histologically, both intralobular and interlobular arteries were involved and, as expected, the infarcts showed complete ischemic necrosis of the parenchyma. Another organ

which showed the picture so characteristic of periarteritis nodosa was the testicle: there was diffuse hemorrhage and grossly visible fine nodules in the spermatic vessels.

Most impressive was the histologic picture of the skeletal muscles. In sections taken from various muscles, the smallest and middle sized arteries showed all stages of the disease (Fig. 43B) from fibrinoid degeneration and marked cellular infiltration to scar formation with thrombotic occlusion of the lumen, quite often already revealing recanalization.

We have here a typical case of periarteritis nodosa, and, histologically, the diagnosis was simple. Far more difficult is the establishment of an etiologic factor. Many factors have been accused of being responsible for this disease. When it first was described, it was considered a specific infection, due, for instance, to a virus. Other investigators considered it not as a specific infection, but as a specific reaction to any of a great number of offenders such as Treponema pallidum or streptococci. We know that vascular changes may be caused by the latter, but they are different from periarteritis nodosa. Then it was suggested that we are dealing with allergic manifestations. To Dr. Rich goes the credit for establishing a firm basis for this belief. He has shown that after treatment with serum or sulfa preparations arteritis in humans may develop and he was able to produce it experimentally in animals. All of us have now seen the arteritic changes after sulfa medication, but some feel that not all cases of periarteritis nodosa belong in this group. In the cases following sulfa medication only the small vessels are involved and acidophilic histiocytes, undetectable in our case, are often found in the organs. We thus cannot be certain that periarteritis nodosa is always an allergic phenomenon; other factors undoubtedly must be considered. I should like to mention that in rheumatic fever arteritic changes are found which are occasionally difficult to differentiate from those seen in periarteritis nodosa and even the role of hypertension in producing these changes has been emphasized.

As you see, a multitude of etiologic factors can be considered but we surely do not know which one applies in the presented case. There seems to be no question that we are dealing in periarteritis with a change of permeability of the vessels whereby some toxic material enters its wall and may even reach the outer layers. We have considered the possibility that certain blood serum constituents which enter the arterial wall may be toxic. We know we can get a positive fibrin reaction within the wall in this condition but we do not know whether this is fibrin from the blood or fibrinoid degeneration of the pre-existent tissue. We are of the opinion at present that the disease, a morphologic entity, is due to permeability changes of the arteries which can be brought about by several different etiologic factors, allergy obviously being one of the most important.

The disease develops in bouts and, morphologically, we can show

in our case the different stages of the condition. The clinical manifestations in periarteritis results from three different causes: (1) toxemia, present in the acute stages of the disease which in this case played the main role; (2) occlusion of the vascular lumen either by thrombosis or intima proliferation leading to ischemic necrosis of various organs—in this case chiefly in the kidney; (3) hemorrhages from perforated aneurysms which have developed in parts of the vascular wall which had been weakened by cellular exudation or scar formation.

In summing up this case and correlating autopsy and clinical findings, we find here different manifestations in various organs as in most cases of periarteritis. There were gastrointestinal manifestations, including vomiting and pain. Three months before death there was an episode of hypertensive encephalopathy and shortly before death the patient was lethargic. The brain was not examined and we do not know whether the hypertension is part of the periarteritis and related to the renal changes, or preceded it. Finally, we have renal manifestations with albuminuria, nocturia and azotemia. The auricular fibrillation may have been related to the hypertension. The cause of death was toxemia, the gastrointestinal, cardiac, renal and central nervous system manifestations being contributory.

Dr. Volini: This interesting case illustrates the difficulty of diagnosis and how frequently the protean clinical manifestations call attention to the diagnosis of specific organ disease rather than the polyarteritis. Actually it is a polyarteritis with extensive distribution of the arteriolar disease throughout the body. We have in this patient the characteristic manifestations of gastrointestinal symptoms, polyneuritis, secondary anemia and wasting and, as in most cases, the greatest focalization of significant symptomatology is in the kidney. Periarteritis nodosa has received wide study. Some authorities make the diagnosis from examination of the eyegrounds; others have reported cases in which proctoscopic examination has permitted the visualization of the specific lesions of periarteritis. I was interested in the lesions in the lung because Herman has claimed that the diagnosis can be made from a study of the chest; that the manifestations of asthmatic bronchitis and the roentgenologic evidence will aid in the diagnosis. This patient did not have complaints referable to the lungs except in the terminal stages. In our experience muscle biopsies have proved disappointing but from the postmortem evidence a definite diagnosis could have been made were time available for this procedure. Positive reports can be obtained in about 25 per cent of cases. Eosinophilia was not present.

I take pleasure in presenting Dr. Aaron Arkin, former attending physician of this hospital and a thorough student of this disease both from the pathologic and clinical points of view. He has contributed extensively to the literature on this subject.

Dr. Aaron Arkin: I am unable to accept this disease as an allergic entity for several reasons. First, the disease has been found in several lower animals, especially in rats and mice. Second, acute periarteritis nodosa is relatively rare in comparison with the thousands of persons suffering from allergic conditions. Third, the disease has an elective affinity for the arterial system. It may involve only a single organ such as the kidney, gallbladder or liver. The possibility of a virus transmission from lower animals to man must still be considered.

The disease is of interest to the neurologist and surgeon as well as the internist. It frequently affects the peripheral nerves leading to foot-drop and wrist-drop. Or it may cause a perirenal hematoma, rupture of the gallbladder, or mesenteric artery occlusion.

The disease is not always fatal. It may affect a single organ with infarction and healing. In rare cases, such as I described in the *American Journal of Pathology* in 1930, it may affect almost every organ with complete histologic healing. The arterial walls are destroyed in segments, with intimal proliferation, aneurysm formation, thrombosis with organization, and extensive periarterial scar formations. A careful study of arterial changes in infarcted organs will no doubt disclose more such cases. Multiple infarctions in the absence of endocarditis or cardiac thrombi speak for periarteritis nodosa.

In the acute disease the chief findings are a septic temperature, polyneuritis and polymyositis, hematuria, abdominal pains, and sometimes palpable subcutaneous nodules or aneurysms of the retinal arteries and negative blood cultures.

Dr. Volini: The term "diffuse vascular disease," as well as polyarteritis, is aptly applied to this condition. Clinically the multiplicity and diffuseness of the presenting symptoms and signs point to the diagnosis of periarteritis nodosa. Fever, wasting anemia, urinary findings, abdominal cramps and polyneuritis appear in irregular order or together. The cardiac symptomatology occasionally dominates the pattern but other apparently unrelated symptoms are usually discernible if sought for.

CASE II. RECURRENT THROMBOCYTOPENIA

Clinical History

Dr. Italo F. Volini: This patient, a white male student aged 16, was admitted to the Cook County Hospital on October 2, 1945 complaining of a petechial rash, epistaxis and hematuria of three weeks' duration. He gave no history of drug intoxication or allergy and no family history of a similar disease. Medical and surgical histories were negative except for the removal of a "growth" from the left popliteal space one and a half years previously.

Laboratory examinations at that time revealed the urine to contain 3 plus albumin and numerous red blood cells. Blood examination showed a hemoglobin of 9.56 gms., red blood cells 2,640,000, white blood cells 8,800 with a differential count of 66 per cent leukocytes, 21 per cent lymphocytes and 13 per cent monocytes; the platelet count was decreased. Sternal marrow study revealed a cellular marrow with an accelerated normoblastic erythropoiesis, showing increased numbers of young megakaryocytes and 38 eosinophils per 1000 granulocytes. The tourniquet test revealed 30 to 40 petechiae per square inch.

A diagnosis of essential thrombocytopenia purpura was made and, after preparation with blood transfusions, a splenectomy was performed. There was some oozing from the wound for several days postoperatively and the platelet count was slow in rising. With the aid of several transfusions, however, the platelet count rose from 2500 per cu. mm. preoperatively to 1,050,000 per cu. mm. nine days postoperatively. He made an uneventful recovery and was discharged.

The patient felt perfectly well until the morning of February 10, 1947, at which time he developed a severe nosebleed which lasted for two hours and required nasal packing for control. He was admitted to Cook County Hospital several hours later. Physical examination upon admission revealed a young man who was not acutely ill but who had a generalized petechial rash over the trunk, abdomen and extremities. His temperature was 98° F., pulse 64, respirations 20 and blood pressure 148/68. Petechiae were also present on the conjunctivae, gums and tongue. Except for the old splenectomy scar, the remainder of the physical examination was essentially negative.

Examination of the blood revealed a hemoglobin of 99 per cent with 5,900,000 red blood cells, 6,650 white blood cells and a differential count of 6 per cent leukocytes, 2 per cent eosinophils, 5 per cent basophils, 56 per cent lymphocytes, 29 per cent monocytes and 2 per cent Türk irritation cells; many of the lymphocytes were atypical; platelet count was 17,700 per cu. mm., coagulation time 15 minutes 20 seconds, and bleeding time was longer than 20 minutes. Bone marrow studies showed adequate numbers of megakaryocytes, and an increase of lymphocytes. The findings were reported as compatible with thrombocytopenic purpura.

The patient's nose was packed and he was placed on a high vitamin diet including vitamin K. He developed a low grade fever for which penicillin was given. More petechiae appeared, and he soon showed red blood cells in the urine. Three days after admission his blood picture showed 87 per cent hemoglobin, 4,700,000 red blood cells, 5,500 white blood cells with a differential count of 5 per cent leukocytes, 1 per cent basophils, 41 per cent lymphocytes and 48 per cent monocytes. His blood was found to be Rh-negative and he was given two transfusions with Rh-negative blood. On the fourth hospital day he suddenly had three bouts of convulsions accompanied by cyanosis. His

temperature rose to 103° F. and he became aphasic. After the last convulsion he became comatose and expired several hours later, on February 15, 1947, five days after his hospital admission.

The clinical summary indicated an apparent recovery from typical thrombocytopenic purpura of idiopathic origin following splenectomy. The hemorrhagic recurrence a little over one year later, again with thrombocytopenia was followed by fatal hemorrhage. The peripheral hemogram indicated a relative lymphocytosis, monocytosis and increased eosinophils. Bone marrow studies aided in ruling out leukemia. Did the patient develop an infectious mononucleosis, or was the lymphoblastic reaction part of an allergic reaction producing the thrombocytopenic purpura? We must ask Dr. Hans Popper for his aid in this quandary.

Pathological Studies and Conclusions

Dr. Hans Popper: Before discussing the autopsy findings, I want to describe the spleen which was removed previously at operation. From the operative notes, it was not markedly enlarged. Histologically, the follicles were of the usual size. Within them were small germinative centers with a few reticulum cells. In the pulp there was slight reticulum cell hyperplasia probably due to hemorrhage; not many megakaryocytes were seen. In general, nothing was found indicative of a splenic disease.

At autopsy, the predominant findings were petechial hemorrhages in the skin and the internal organs wherever we looked. In the mediastinum there was a large mass of blood infiltrating the connective tissue below the sternum. Also, under the pleura, flame-shaped and confluent hemorrhages were noted everywhere. Hemorrhages were also found within the lung, below the epicardium and peritoneum, in the mucosa of the renal pelvis and stomach and intestine. An extensive hemorrhage in the left basal ganglia broke into the ventricle and was obviously the cause of death (Fig. 45).

In order to explain this catastrophic flare-up of a hemorrhagic diathesis, the parenchymal organs were examined thoroughly under the microscope. The liver did not show much except for some nonspecific periportal infiltration. The spleen was, of course, absent at autopsy, but we found three accessory spleens—one of about cherry size, the other two smaller. They revealed nothing of significance. The pulp showed even less response to the hemorrhage than did the previously removed spleen. There was generalized adenopathy involving the axillary, inguinal, hilar, perigastric and periaortic nodes. The nodes were up to 3 cm. in diameter, discrete, soft, on the cut surface gray with purple patches. Histologically, their architecture was obliterated. There was a diffuse scattering of lymphocytic and lymphoblastic elements throughout the entire field. Some of the lymphoblastic elements were large and occasionally giant cells were seen. Between them was

a variable number of eosinophils, sometimes scattered, sometimes densely arranged, almost in groups. The reticulum cells revealed little proliferation (Fig. 46*A*).

The bone marrow was very cellular. In low power examination a large number of megakarocytes was readily noted, which is in keeping with the diagnosis of thrombocytopenic purpura. It is usually believed that, in this condition, the ability of the megakaryocytes to form platelets is impaired and some have claimed that they may be pathological

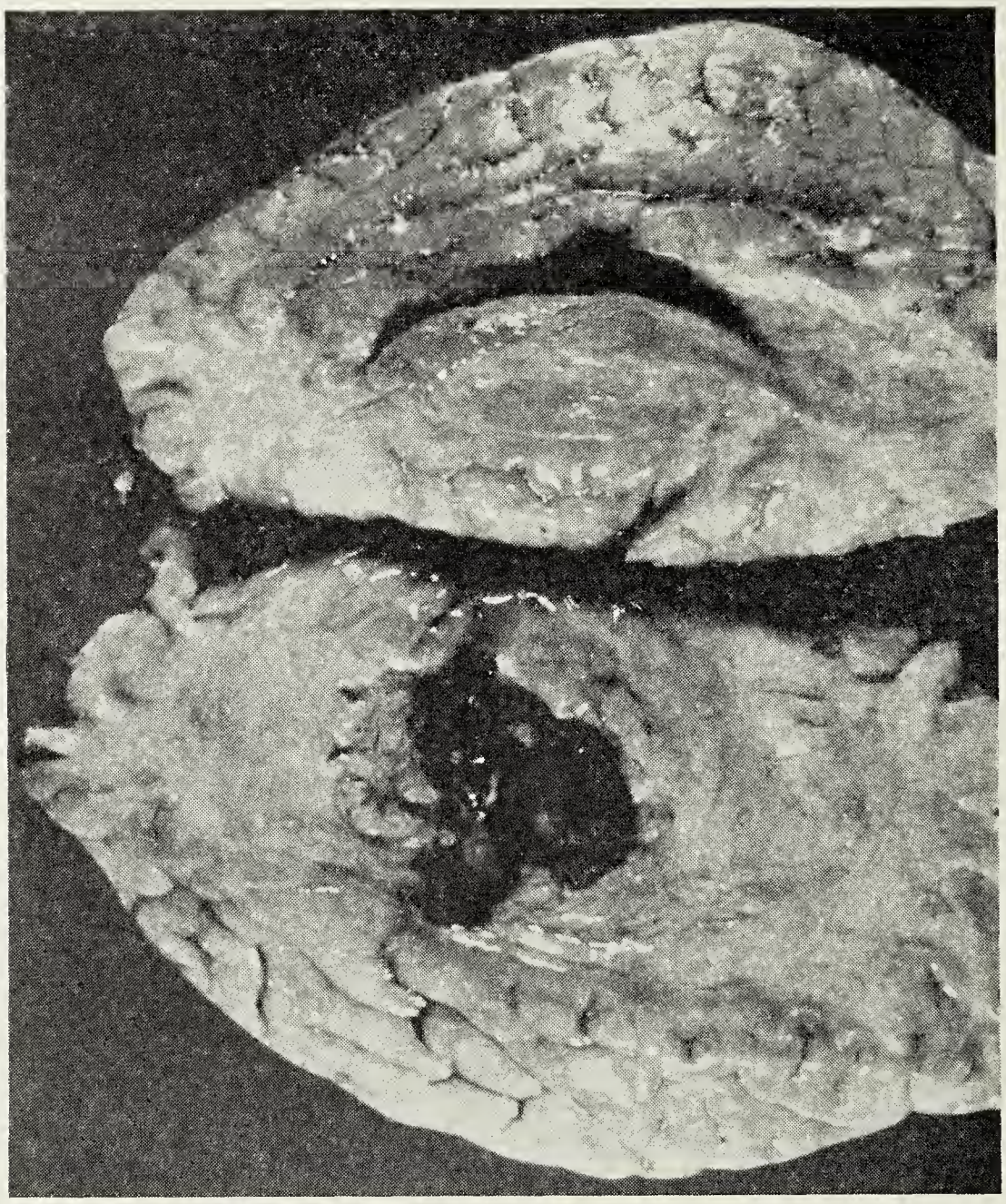

Fig. 45.—Extensive recent hemorrhage destroying the left basal ganglia and breaking into the lateral ventricle.

in appearance. Although atypical forms were seen, I am reluctant to draw any conclusion from paraffin slides. There were small focal accumulations of lymphocytes. In discussing this with Dr. Schwartz, he considered it an incidental finding and I also believe it is a physiologic variant. In addition, there were diffusely scattered lymphoblastic elements, polymorphic in character, and a fairly dense sprinkling of eosinophils (Fig. 46B). A smear from the cadaver blood showed a large number of unusual cells, best interpreted as lymphoblasts.

In an attempt to analyze this somewhat peculiar case, we find two obvious problems. I am not too sure whether we can answer both of them satisfactorily. First, we have a thrombocytopenic purpura which was, when originally seen, quite typical in character. One and one-half years before death there were no atypical cells in the blood or

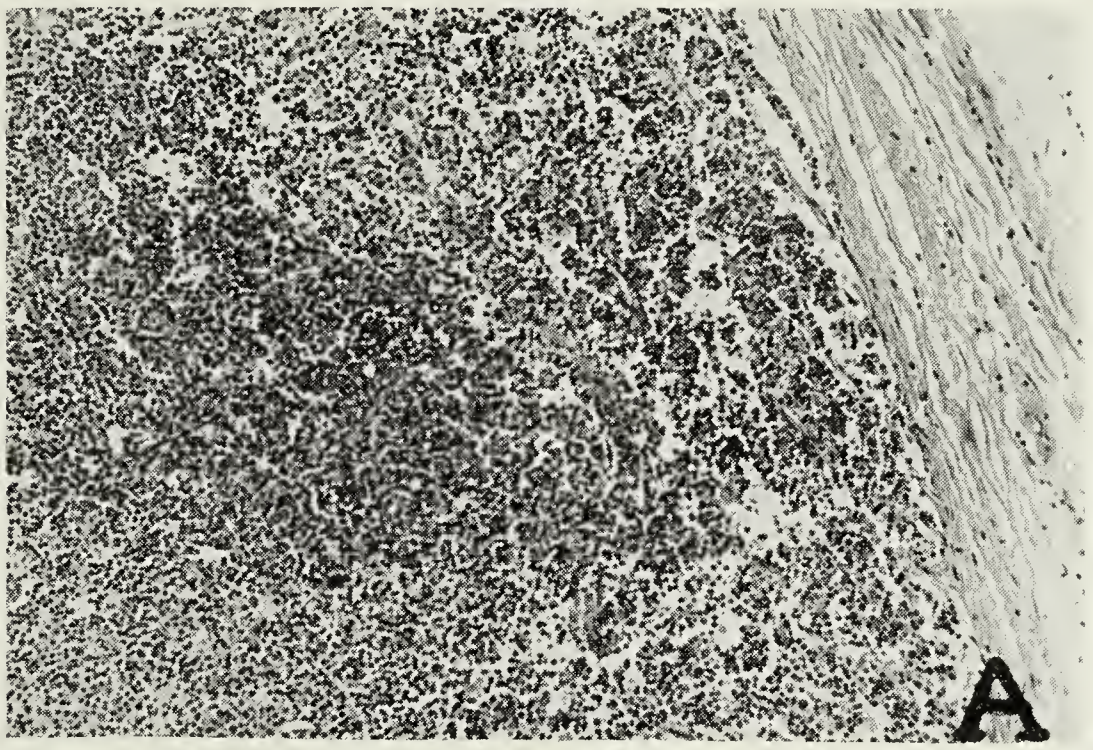

Fig. 46.—*A*, Lymph node revealing obliteration of architecture. Diffuse infiltration by lymphocytic and lymphoblastic elements. *B*, High power view of the cellular bone marrow in the femur. Many megakaryocytes are seen, some of them of atypical appearance. A large number of lymphocytic and lymphoblastic cells are found throughout.

spleen. There was no eosinophilia, no allergy was present, and splenectomy was followed by the expected cure. The patient was in a very good condition until suddenly a recurrence developed which was fatal as the result of a brain hemorrhage. This is a typical and common cause of death in thrombocytopenia. What was, however, the cause of

this recurrence? The peculiar lymphoblastic reaction is not part of an ordinary thrombocytopenia. Some of the cells in the blood smear were considered monocytes by the hematologist. Obviously, given a patient with a severe reaction of this kind, one's first thought is leukemia in which thrombocytopenia commonly does occur. However, no morphologic evidence of leukemia whatsoever was found in the organs at autopsy, confirming the previous findings of the hematologic department.

The second diagnosis which may suggest itself is infectious mononucleosis. In this disease the thrombocytes are occasionally significantly reduced and hemorrhages may occur. I could possibly accept this diagnosis from the study of only the bone marrow and lymph nodes, but there was nothing, either in the originally removed spleen or in the accessory spleens at autopsy, which would support this diagnosis. Without splenic changes, a diagnosis of infectious mononucleosis with thrombocytopenia is surely untenable. Minot has recently described episodes of marked lymphocytic reaction in cases of thrombocytopenic purpura. In these cases the patients survived the thrombocytopenia and the lymphoblastic reaction subsided. We may be dealing with a similar condition in our case. Minot felt that it was due to a peculiar reaction to infection and reports fever in his cases. Our patient had fever although it could be explained as a response to the hemorrhage. It has been called to our attention that this infection may have been associated with allergy. This appeals to me as a possibility because of the eosinophilia.

In summing up this case, on the basis of the presented evidence, we are dealing with a case of thrombocytopenic purpura in which the patient recovered after splenectomy. One and one-half years later there was a fatal recurrence associated with an unexplained lymphoblastic reaction. The latter may be on the basis of a peculiar inflammatory reaction possibly due to infection and may be associated with allergy in view of the eosinophilia present. I want to conjecture that this lymphoblastic reaction is the cause of exacerbation of the thrombocytopenic purpura in a way I cannot explain.

Dr. Italo F. Volini: It seems as though Dr. Steven O. Schwartz, attending hematologist at Cook County, must analyze the evidence still further for us.

Dr. Steven O. Schwartz: Let us go back to the first admission of patient to the hospital and discuss what we did, and also what we could and should have done.

We believed, on the basis of marrow examination, that this was an essential type of thrombocytopenia with a full marrow, no evidence of marrow displacement, an adequate number of megakaryocytes and no increase of eosinophils to indicate that the condition might be allergic in etiology. There are three reasons for examining the marrow: (1) to

rule out the possibility of the thrombopenia being secondary to marrow displacement; (2) to prognosticate what the response will be after splenectomy; and (3) to determine whether the etiology is allergy. We were satisfied that this patient was a candidate for splenectomy and after transfusions he was operated upon. We were distressed because the platelet count was slow in rising but it eventually rose to nearly 2,000,000.

We saw the patient periodically in the clinic and on December 4, 1946 he had a 700,000 platelet count, 8,000 white blood cells, 5,400,000 red blood cells and a normal differential count. Two months later he reappeared with 5,900,000 red blood cells, a normal white blood cell count but only 17,000 platelets. At this time he had a great number of lymphocytes and monocytes. Naturally we speculated on the reason for the recurrent thrombocytopenia. The first possibility was that there had been a recurrence of splenic tissue, which takes place occasionally. Against this was the precipitous drop in platelets. The second possibility was that an acute leukemia had developed. Against this was the normal red cell count and, though the white count did not help, subsequent examination of the marrow ruled this out. The third possibility, which Dr. Popper has mentioned, was that this was a case of infectious mononucleosis. The interesting thing is that in every case in which thrombocytopenia has been described in infectious mononucleosis the spleen was incriminated, and when the spleen was removed the thrombocytopenia disappeared, so even if we assume this to be infectious mononucleosis we still have to explain why the patient had a recurrent thrombocytopenia.

We actually do not know what thrombocytopenic purpura is. We assume that it is usually mediated through some splenic mechanism which can do one of two things: (1) It can produce a substance—a hormone perhaps—which inhibits marrow activity. This inhibition may be along a single line and may result in the inhibition of megakaryocytes. This inhibition may be bilateral or it may involve the entire marrow and be pancytodepressant. (2) Or the spleen acts as an organ to screen out certain elements; sometimes the platelets, sometimes red cells, sometimes white cells. The fact that there are more than the usual number of megakaryocytes does not help us distinguish between the two types because, whether there is inhibition or a screening out, the megakaryocytes would hypertrophy. Most of us feel that the probable explanation is an inhibition of platelet formation at the level of the megakaryocytes.

We are satisfied that the thrombocytopenia is mediated by way of the spleen (in thrombocytopenia purpura), but this boy had thrombocytopenia the second time and did not have a spleen. The small accessory spleens are not adequate to explain the recurrence and, even if they were, we would still have to explain the tremendous lymphoid hyperplasia and infiltration of the marrow and lymph nodes.

Two explanations are offered: (1) The condition was an atypical response to infection which would explain the lymphocytosis and at least would give us a pathologic basis of explanation, although it may not be satisfactory physiologically. (2) In allergy we can have thrombocytopenia also. This may be cured by splenectomy or without splenectomy if the allergen is removed. Whether our patient had allergy at first is doubtful, but the second time he did as indicated by the tremendous tissue eosinophilia. I doubt that this allergy had anything to do with the transfusions because there was no evidence of the eosinophilia until his second admission. If we assume that this was hypersensitivity then we know that lymphoid hyperplasia can also occur on a similar basis. Occasionally this can be very acute. We do not know very much about what happens histologically during these acute lymphoid hyperplasias because ordinarily the patients do not die and are not biopsied. If this boy had an allergy and developed a lymphoid hyperplasia, then we may further assume that these hypertrophied lymphoid tissues liberated or manufactured a substance not dissimilar to what the spleen ordinarily produces and therefore, acted as splenic organs (which are actually lymphoid organs).

Dr. Hans Popper: I am very pleased about the agreement in the interpretation of this puzzling case. I am glad that Dr. Schwartz provided the missing link which permits me to understand the case much better. If we accept it as an allergic reaction, I would still like to stress that the morphologic picture is different from the allergic reaction we usually see, for instance, in sulfa treated cases. I, therefore, feel that we should emphasize a peculiar inflammatory reaction in addition to the allergy.

Dr. Volini: There are many atypical features in this case. The patient had this change in the qualitative peripheral blood count, eosinophils in the sternal marrow aspiration, a relatively slow rate of rise of platelets after operation, relapse without a very pronounced finding of enlargement of these accessory spleens and a rather low platelet count on second admission to the hospital.

I should like to say something about the possibility of allergic sensitization. This patient received many transfusions and it was not mentioned that the Rh factor was negative during his first admission. It was during the second study that this was noted and it may be that he received Rh positive blood during his first period in the hospital.

There are so many ways that we can miss information about allergy in our studies. The history in this case definitely states that the patient was not allergic and that there was no history of drug sensitization. We know many of the drugs, particularly the antibiotics, would have a very pronounced effect in this particular case, but I wonder if any inquiry was made as to whether this boy had had injections for the

many immunizations which are commonly used today. In a case like this it is necessary that we inquire thoroughly and minutely into his history. I can state quite definitely that lymphocytic or lymphoblastic phenomena occur subsequent to or during the course of an allergic reaction. When we were treating pneumonia patients with rabbit serum we frequently found a generalized lymphadenopathy with splenic tumor. It is apparent therefore that a generalized lymphocytic reaction can occur.

SUBACUTE BACTERIAL ENDOCARDITIS: ETIOLOGIC CONSIDERATIONS AND PROPHYLAXIS

Paul S. Rhoads, M.D., F.A.C.P.*

Since confusion exists in the terminology used in infectious endocarditis, we shall begin by delimiting the present discussion to that type in which the responsible organism is usually one of relatively low virulence and in which the patient survives longer than six weeks. In more than 90 per cent of cases the micro-organism causing subacute bacterial endocarditis is a nonhemolytic streptococcus of either the alpha or gamma types. Formerly the course of the disease was from several months up to one and one half or two years before fatal termination. With the present method of treatment more than half of the subjects survive. On the other hand *acute* bacterial endocarditis—which will not be mentioned further in this communication—is usually caused by the pneumococcus, hemolytic streptococcus or Staphylococcus aureus and runs a rapidly fatal course, seldom exceeding six weeks. Rarely one of the organisms just mentioned, of attenuated virulence, may be causative in the subacute form of the disease.

At various times all of the micro-organisms listed in Table 1, usually singly but occasionally in combination, have been cultured from the

TABLE 1

Micro-organisms Cultured from the Blood and Heart Valves in Subacute Bacterial Endocarditis

Streptococcus viridans	more than 90 per cent of cases
Streptococcus anhemolyticus	
Gonococcus	
Meningococcus	
Micrococcus pharyngis siccus	
Brucella (all types)	
Hemophilus influenzae and para-influenzae	
Streptococcus moniliformis	
Spirillum mitis	
Micrococcus tetragenus	
Streptococcus hemolyticus	of lowered virulence
Pneumococcus	
Staphylococcus aureus and albus	

blood of patients thought to have subacute bacterial endocarditis and there seems no good reason to doubt that most of them have caused

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the typical endocardial vegetations which characterize the disease. There would be less confusion if the terms "acute vegetative" and "subacute bacterial endocarditis" were abandoned and the term infectious endocarditis qualified by the name of the responsible microorganism were used.

A brief review of the known facts regarding the genesis of subacute bacterial endocarditis will serve best as the starting point for theoretical considerations. It is generally agreed that, (1) with rare exceptions, the vegetative lesions of subacute bacterial endocarditis became implanted upon the valves and mural endocardium in hearts in which previous pathologic changes in the valves or congenital endocardial defects are present. (2) The precipitating cause is the entrance of one of the bacteria mentioned in Table 1 into the blood stream, with subsequent implantation upon the valves. Sometimes the connection between an active focus of infection and the endocardial lesions appears to be quite direct. In other cases no demonstrable focus of infection is present. (3) Some property of the valve lesions in subacute bacterial endocarditis protects the causative organism from the ordinary sterilizing influence of humoral antibodies and phagocytes, and to a great extent from all forms of chemotherapeutic and antibiotic agents. Hence, once established, the vegetations continue to grow. As small portions of them break away into the blood stream, bacteremia and blocking of end arteries by small emboli in various parts of the body result.

A consideration of the morbid processes operating to produce this train of events may suggest means of prevention.

PREVIOUS VALVULAR DAMAGE

In all reports of large series of subacute bacterial endocarditis cases necropsy has revealed the presence of previous valvular damage in all but a small percentage. When bacteria containing vegetations form on previously undamaged valves the infection usually is with microorganisms of unusual inherent virulence, such as hemolytic streptococci or pneumococci. If bacteria of less virulence, such as Streptococcus viridans, cause endocarditis in previously undamaged hearts usually it is because they enter the blood stream in extremely large numbers and over a considerable period of time.

Rheumatic heart disease has been reported as the predisposing factor in proportions varying between 64.5 and 89 per cent in various series.[1, 2, 3] In thirty patients with subacute bacterial endocarditis at Wesley Memorial Hospital in the past five years rheumatic heart disease was inferred from the history, or proved at autopsy in twenty-five patients (83.3 per cent).

Several clinicians have pointed out the relative infrequency of endocarditis in persons with congestive failure due to rheumatic heart disease (Libman and associates,[4] Christian[3] [6.66 per cent of cases],

Keefer,[5] Middleton and co-workers[6] [5.6 per cent]), emphasizing the fact that the disease is much more apt to occur in those rheumatic subjects whose cardiac function is above average. If one considers the large number of well compensated cases of chronic rheumatic heart disease as compared to those in failure the proportion reported by these authors does not appear significant. Certainly the implication in the statements of Christian and Keefer that decompensation appears to offer some degree of protection from bacterial endocarditis hardly seems justified.

Congenital heart disease has proved to be the next most important group, numerically, in furnishing the background for subacute bacterial endocarditis, being present in 5 per cent in both White's[2] and Christian's[3] series, and being mentioned in practically all large series. Some idea of the frequency of subacute bacterial endocarditis in persons who have congenital heart disease can be gained from the figures of Maude Abbott,[7] who found that among 446 such persons who came to autopsy 16 per cent had endocardial vegetative lesions. In a series of 453 congenital heart lesion subjects who were autopsied, Gelfman and Levine[8] found subacute bacterial endocarditis in 6.5 per cent of the entire group and in 16.5 per cent of those under two years. While most any type of congenital defect may be the site of vegetative lesions, patent ductus arteriosus, defective interventricular septum, bicuspid aortic valves and coarctation of the aorta are the most common.

Syphilitic aortitis and arteriosclerotic involvement of valves and mural endocardium together probably account for less than 1 per cent of the predisposing lesions in subacute bacterial endocarditis. The combination of these conditions with rheumatic heart disease constitutes the "determinative background" (Christian) more frequently than either of the conditions alone. Lemann[9] reported an interesting case in which the mitral valve had been made insufficient by infarction of the left posterior papillary muscle due to coronary artery thrombosis.

THE PRECIPITATING EVENT

The precipitating event which eventuates in vegetations upon the valvular or mural endocardium is often less easily recognized than the "background" pathologic changes. Indeed, more often than not, no definite precipitating factor is recognized, the patients' only complaints being continuing fever and increasing fatigue, weakness and anemia in the absence of any immediately preceding infection. However, clinical studies indicate, and experimental studies prove that bacteria must enter the blood stream in appreciable numbers and, in some way, become implanted upon the valves. The mechanism of this implantation will be referred to later.

To Rokitansky[10a] has gone the credit of first reporting bacteria in the valve lesions of endocarditis. Winge,[10b] in 1869 reported to the Norwegian Medical Society an autopsy in which the typical cardiac

and embolic lesions of infectious endocarditis were associated with a suppurative lesion of the little toe at the site where a corn had been torn out. He surmised that the lesion of the toe was the focus from which endocarditis resulted. His associate, Heiberg,[10c] three years later reported a similar case in which streptococci were seen in the vegetations and in which the original focus was an infected postpartum uterus. Since these pioneer observations the medical literature has been augmented by hundreds of reports in which the development of endocarditis followed so closely upon the probable dissemination of a micro-organism—usually Streptococcus viridans—from a recognizable focus of infection that the circumstance was clearly more than fortuitous. In subacute bacterial endocarditis the principal recognized foci are the upper respiratory tract (including tonsils and sinuses), infected teeth and gums, nonspecific prostatitis, infected hemorrhoids and urinary tract infections. Frequently Streptococcus viridans endocarditis appears to be the terminal event in chronic wasting diseases, such as cancer, pyelonephritis from prostatic obstruction, polycystic disease of the kidneys, and the like. Operative manipulation in the areas mentioned frequently causes a transient bacteremia, but in some instances—such as acute tonsillitis or acute pyelitis—bacteremia occurs as a part of the infection. In the Wesley Hospital series of thirty cases a preceding infection of the upper respiratory tract was found in eleven instances, a recent tooth extraction in six and a urinary tract infection in one. There were twelve cases in which no precipitating infection could be discovered. Richards[11] showed that massage of infected joints, tonsils, gums and prostates resulted in a positive blood culture in a significant number of cases. Round, Kirkpatrick and Hails[12] studied patients with advanced gingivitis and found that such persons had blood cultures positive for Streptococcus viridans and Staphylococcus aureus, following the chewing of mint candies.

In a current study Miss Doris Adair and I have performed blood cultures, by various technics, in twenty-five instances at intervals of ten minutes, three hours, and twenty-four hours after tooth extractions. In eight of the cases (32 per cent) positive cultures have been obtained. These results confirm those of numerous investigators who have reported similar findings in 10 to 75 per cent of the subjects tested.[14,15]

EXPERIMENTAL ENDOCARDITIS

A disease simulating subacute bacterial endocarditis, both in the clinical course and postmortem findings, has been produced repeatedly in laboratory animals—especially the rabbit and dog—by intravenous inoculations of Streptococcus viridans. Rosenow[16] felt that a much higher incidence of the experimental disease could be obtained by using streptococcus cultures from the blood of patients suffering from the disease. Other workers showed that the source of the streptococci was unimportant, those usually regarded as harmless saprophytes in

the oral cavity or intestinal tract of normal persons being capable of inciting the disease in animals if given in large enough quantity over a long enough period.[17, 18, 19] Still other investigators have tried methods which they considered simulated better the train of events in human endocarditis. Injection of viridans steptococci was preceded by "preparation" in various ways—such as mechanical traumatizing of the heart valves or mural endocardium with a wire or hypodermic needle;[20] injection of aleuronate intravenously to injure and vascularize the valves;[2] creation of a subcutaneous focus of the streptococcus later to be injected intravenously; intravenous injection of casein, pituitrin, lithium carmine and other preparations to injure the endocardium; production of scurvy by dietary restriction.[4] After such "preparation" it was found that injections of Streptococcus viridans need not be as large or over as long a period for successful results in producing vegetations.

Some years ago, Dr. Herbert H. Kilgore and I injected Soricin (sclerosing solution) in small amounts into the heart muscle near the valve attachments in rabbits. Beginning the same day and continuing at intervals of twenty-four to forty-eight hours Streptococcus viridans strains from subacute bacterial endocarditis were injected in doses of 1 to 2 cc. Several typical vegetative endocardial lesions were produced, which acted as the site for multiple emboli in the experimental animals.

An experiment of Friedman, Katz and associates[22] is of interest in explaining the invulnerability of the bacteria of endocardial vegetations to the action of antibodies, phagocytes and drugs. They suspended in the blood stream of the abdominal aorta of seven dogs a small bakelite capsule filled with a blood agar culture of Streptococcus viridans and perforated at the free end. In two of the animals the capsules became completely covered with fibrin, so that polymorphonuclear leukocytes could not gain entrance. In the other animals the capsule cultures did not survive. However, in the fibrin-covered capsules the streptococci flourished and vegetative lesions developed on the heart valves of the hosts. Thus enmeshment in a fibrin mass appeared to provide the microorganisms with the pabulum they required for rapid growth and at the same time protect them from the various mechanisms by which germs not so protected are destroyed.

THE MECHANISM OF VEGETATION FORMATION

The vegetations of bacterial endocarditis appear most frequently on the ventricular sides of the aortic and mitral valves at the point where the free edges of the cusps meet as the valves close, hence at the point of greatest mechanical impact. According to Moore,[23] any of the valves may be involved but mitral vegetations due to Streptococcus viridans are ten times as frequent as tricuspid and twenty-seven times as frequent as pulmonic vegetations. Aortic vegetations are about

seven times as frequent as tricuspid and eighteen times as frequent as pulmonic lesions. Frequently the mural endocardium just above or below the mitral valve and the chordae tendinae of the atrioventricular valves are the sites of vegetations. In typical bacterial endocarditis, microscopically it is seen that immediately adjacent to the valve surface there is a zone comprising from one-half to two-thirds of the vegetation which is composed of necrotic debris with few living cells. This zone contains fibers of collagen and some elastic fibrillae. Young fibroblastic tissue and capillary vessels are seen growing into this zone. Above the first zone is a narrower one containing colonies of bacteria in rather dense masses and surrounded by fibrin. Above this middle zone is a layer of fibrin in which are enmeshed a number of polynuclear leukocytes and red blood cells. This fibrin as a rule completely protects the bacterial clumps from phagocytosis. Since there is no general agreement as to the manner in which these lesions develop, several of the current theories will be mentioned.

1. Clawson and Bell[24] proposed the idea that rheumatic fever and subacute bacterial endocarditis represent respectively mild and severe forms of the same disease. This idea was thought to be substantiated by the finding of a nonhemolytic streptococcus of low virulence in the blood cultures of a small number of patients having acute rheumatic fever, and the same organisms of heightened virulence in the majority of those in which the disease supposedly advanced to the condition recognized as endocarditis.

As pointed out by Willius,[25] this idea seems untenable, first because many organisms which have never been associated clinically with rheumatic fever, such as H. influenzae, B. abortus and so forth have been proved as the responsible agent in some cases of subacute bacterial endocarditis; and secondly, because the endocardial lesions have been found in hearts which have never been the site of rheumatic lesions, for example, those of congenital and syphilitic heart disease.

2. Von Glahn and Pappenheimer[26] contended that *active* rheumatic endocarditis was an essential prerequisite to the occurrence of bacterial endocarditis, although the active unhealed lesions may have been present for extremely long periods before the vegetations developed. In support of this view they showed specimens in which both processes were present in the same valve. Usually, however, the simultaneous presence of the two types of lesions is not found. Also the concept fails to explain the presence of subacute bacterial endocarditis in hearts not the seat of rheumatic changes.

3. Many persons believe that small bacterial emboli originating in foci of infection reach the valve leaflets through capillaries growing into the valves from the myocardium (Hildebrand and Priest,[27] Held and Lieberson[28] and others). Due to a state of hyperimmunity and increased local resistance in the valves which already are chronically diseased the usual response to infection does not occur. Instead of an

exudation containing many leukocytes, ulceration and subsequent connective tissue formation, there is a deposit of fibrin and blood platelets which attracts, furnishes pabulum for and protects the microorganisms.

Attractive as this theory is it does not have general acceptance because there is no agreement that all heart valves of adults are vascularized, even though there has been previous valvular damage. Harper[21] has shown that vascularization of valves may occur from intravenous injections of aleuronate into rabbits without the simultaneous injection of bacteria, and he believes that other extraneous material in the blood stream may have the same effect. Hence in a prolonged bacterial infection vascularization could occur as the result of nonspecific injury; but he concludes that this process is an *accompaniment* of the implantation of bacteria on the valve surface and not the *cause* of the endocarditis. Much evidence points to the implantation and focalization of bacteria on the surface of the valve from the blood stream rather than from embolization of the valves.

4. Grant, Wood and Jones[29] in an important contribution found that previously damaged heart valves had surface irregularities which did not in themselves offer a site for implantation of bacteria but which offered a location for the lodgement of platelet thrombi, which, in turn, attracted and held bacteria. Semsroth and Koch[30] found nodular, monocytic proliferations in the zone just beneath the intact valvular endothelium. They believed that these nodules later regressed, causing endothelial defects which became the site of thrombi upon which bacteria from the blood stream became localized.

5. The location of the lesions has indicated to many students the importance of mechanical factors. Allen,[31] Libman[4] and others have pointed out that the undersurface of stenotic mitral aortic valves which receive the maximum force exerted by the left ventricle on its contained blood are the most frequent sites for localization of vegetations. These parts of the mural endocardium upon which blood very forcefully impinges—such as the wall of the right ventricle opposite a small interventricular defect and the rim of such a defect, frequently become the sites of vegetations. How this repeated trauma results in implantation of the bacteria is not clearly understood, but that it plays a role seems indisputable from clinical observation.

6. Finally, the immunity status of the patient at the time of the initiating bacteremia requires careful consideration. Swift[32] suggested that streptococcal infection in a person who is hypersensitve resulted in rheumatic fever while subacute bacterial endocarditis was the outcome if the subject was immune. While this possible oversimplification has much merit, Libman has raised the objection that occasionally subacute bacterial endocarditis and rheumatic fever occur simultaneously in the same patient and even on the same valve.

Keefer[5] and others have observed that antibodies capable of de-

stroying the responsible organisms in vitro are frequently present in the blood of subacute bacterial endocarditis patients. Kinsella and Muether[20] produced endocarditis in dogs previously immunized to the micro-organisms being inoculated and in animals receiving hyper-immune serum at the time of experimental inoculation. Apparently the micro-organisms are easily destroyed in the blood stream by the combined action of antibodies and phagocytes. Continued bacterial proliferation on the heart valve can occur because, owing to the protective film of fibrin on the outside and the inability of blood to reach the bacterial masses from the valve surface, phagocytosis of the micro-organisms does not take place. Continued reinfection of the blood steam results from breaking loose of small masses of infected thrombi.

PROPHYLAXIS

Real progress in the prevention of subacute bacterial endocarditis requires imagination. There is no way of predicting what the expectancy for this disease will be in rheumatic subjects. However, when it is realized that approximately 16 per cent of persons with congenital heart disease who come to autopsy have a subacute superimposed bacterial endocarditis, the hazards of transient bacteremias in that group should be apparent to everyone. The danger of this development in persons with active or inactive rheumatic heart disease is no less real. In individuals with syphilitic or arteriosclerotic heart disease subacute bacterial endocarditis is likewise a threat but a less serious one. If cognizance is taken of the various types of heart damage which predispose to bacterial endocarditis and the possible sources of entry of bacteria into the blood stream are recognized, much can be done in prevention.

In the long run the most important step in preventing this disease is the *prevention of rheumatic fever.* Present studies would indicate that prompt recognition and vigorous treatment of all hemolytic streptococcus infections and prolonged supervision of the persons suffering from them constitute the most useful measures in that direction. If both the public and the medical profession could become fully aware of the sequelae of prolonged and neglected infections of the respiratory tract, patients would not be returned to their usual pursuits twenty-four hours after the temperature has become normal. Instead, cultures of the nose and throat, blood counts and sedimentation rates would be made routinely on all persons with infections of the upper respiratory passages. Termination of medical care would be made on the basis of negative cultures for hemolytic streptococcus and other pathogens and on clinical and laboratory evidence that the infection had subsided. Such evidence includes disappearance of redness and lymphoid hyperplasia of the pharynx, and of enlarged cervical lymph nodes, together with return of blood counts and sedimentation rates to normal and disappearance of albuminuria. In a follow-up study now

being made at Cook County Contagious Hospital, we are finding by these simple criteria that the infectious state following scarlet fever often persists as long as three months after the patient has become afebrile.

A rekindling of interest in *focal infection* would also do much in the prevention of subacute bacterial endocarditis. And in this regard once more the great need for anticipating the consequences of continued slight infection merits re-emphasis. Foci should be eliminated before they have acted over a long period as sensitizing foci from which bacterial toxins are spread or as atriums from which bacteria are disseminated into the blood stream. In subjects with known valvular heart disease, removal of such foci before vegetations are set up is of paramount importance.

Before the advent of sulfonamides and penicillin the risk of surgical removal of tonsils and teeth, washing of antrums and similar procedures in known rheumatic subjects had to be weighed carefully against the risk of leaving them in. At the present time, if surgeon and internist will cooperate intelligently, the surgical risk can be minimal. In our own series of blood cultures taken immediately after tooth extractions made under the protection of sulfonamides or penicillin, we have had no growth. The series (twenty cases) is too small for clinical conclusions but it seems most likely that a good therapeutic blood level of either agent will take care of any transient bacteremias that occur under these circumstances. That this program is not entirely foolproof, however, is shown by a series studied by Northrup and Crowley.[33] In seventy-three persons under treatment with sulfathiazole given in doses of 1 gm. at intervals of four hours up to one to two hours before tooth extraction, streptococci were cultured immediately after the operation in seven instances, but not ten minutes later. In five of these instances the sulfathiazole level was less than 3 mg. per 100 cc. of blood, two were in persons whose level was 3.5 to 5 mg. per 100 cc. As in every other medical procedure the need for careful and adequate therapy is evident.

Our own plan in dealing with persons known to have chronic rheumatic heart disease is to hospitalize the subjects for tooth extractions, antrum washings, tonsillectomy, and related procedures, if possible; they are then given penicillin by intramuscular injection of the aqueous solution in doses of 25,000 to 40,000 units every three hours beginning at least four hours before the surgical procedure and continuing for at least thirty-six hours afterwards. When hospitalization was not possible we have frequently given 300,000 units of penicillin in oil and beeswax a few hours before tooth extraction and again twelve hours later. No bacteremia has resulted after these procedures but twice we have encountered severe allergic reactions to the penicillin in oil and beeswax. When sulfonamides have been used we have usually chosen sulfadiazine, starting with an initial dose of 3 gm. and

following with maintenance doses of 1 gm. every four hours for forty-eight hours, administering 3 gm. of sodium bicarbonate with each dose.

The prompt use of either penicillin or sulfonamide in all respiratory infections and thrombophlebitis—even of a minor nature—in subjects with rheumatic or congenital heart disease and these measures or streptomycin in urinary tract infection also needs emphasis. Continuation of the therapy for as long as *all* signs of persistent infection remains is important.

SUMMARY

Intelligent prophylactic measures against subacute bacterial endocarditis depend upon a recognition of the underlying pathologic changes in the heart which serve as the determinative background for this disease. These changes chiefly are those present in chronic rheumatic valvular disease and congenital defects of the valves and heart chambers, although arteriosclerotic and syphilitic heart disease in rare instances are implicated.

The precipitating cause is the entrance of bacteria (usually nonhemolytic streptococci) into the blood stream with subsequent localization on the heart valves. Prevention of this bacteremia by removal of foci of infection under the protection of vigorous sulfonamide or antibiotic therapy, and by similar treatment of spontaneous infections which may eventuate in bacteremia, is the physician's duty.

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THE PRESENT STATUS OF SYMPATHECTOMY IN THE TREATMENT OF HYPERTENSION

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During the past two decades, and more particularly during the latter half of this period, interest in a specific attack upon the medically and economically potent problem of hypertension has absorbed a large share of attention from all special branches of medicine.

The reasons for this swing in interest are apparent when one studies the statistical material available through the acturial efforts of different life insurance groups.

With progress in the fields of specific and symptomatic therapy for diseases which formerly enjoyed a high rating in the list of "causes of death," the hypertensive state has come farther to the front until it now enjoys first position. Furthermore, in keeping abreast with the pace set by his creations in practically all fields of endeavor, man has automatically, below the level of consciousness, adjusted his performance to a faster, finer strung and more bewildering tempo than his autonomic nervous system is capable of serving at this stage in his evolution.

The psychological factor is a major barrier in the successful medical management of the majority of hypertensive patients. Most of them are at the peak of their productive years. It is neither psychologically nor economically sound, or in most instances possible, for them to assume the role of semi-invalid which is a requisite of good medical management.

RATIONALE FOR SURGICAL TREATMENT

This line of reasoning calls for clarification of the etiological factors contributing to the hypertensive state. A concise picture cannot be drawn. It is well known that the cause of arterial hypertension is a complexity of neurohumoral factors working in combination and sequence.

We (Peet and associates) believe that the prime factor in the perpetuation of the hypertensive state is the physiologic Goldblatt[1, 2, 3] "clamp" effect upon the efferent vascular bed to the kidney and that the splanchnic pool or shunt plays a secondary role. There is suggestive clinical laboratory evidence, deductive in nature, that this is true.[4, 17] Further work is necessary to prove or disprove this hypo-

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thesis. The "clamp" is induced by vasopressor stimuli arising in the hypothalamus, which system responds in this fashion to pertinent stimuli either exogenous or endogenous in origin. Sympathectomy removes the "clamp." The hypothalamic factor is quite generally accepted and has been demonstrated in the laboratory[5]. An attack upon the problem of arterial hypertension by way of the hypothalamus would seem logical though with our present gross technic not feasible. Methods for such a technic are at present being investigated.[6]

Others[7, 9, 11] believe that the effectiveness of surgical ablation of sympathetic stimuli to the vascular bed of the splanchnic area is brought about by the creation of a vascular shunt or pool in the abdominal viscera and lower extremities and that the renal effect is of lesser importance in the overall picture. Grimson[9, 10, 30] believes that not only the splanchnic bed but the pulmonary, cardiac and cerebral vascular beds should be sympathetically denervated as well. Poppen[11] follows Smithwick's views in the matter of the purpose of surgery and has extended his technic cephalad, the emphasis being an attempt at prevention of regeneration of efferent sympathetic pathways and more complete eradication of the ubiquitous so-called anomalous ramifications of the thoracic chain and its contributions to the splanchnic system.

It must be borne in mind that we are considering here arterial hypertension per se and not hypertension induced by unilateral kidney disease, obstructive uropathies, adrenal or chromaffin cell tumors or brain tumors.

SELECTION OF CASES

As more and more hypertensives are treated surgically, pre-existing rigid criteria for selectivity have been modified, thus allowing the benefits of such treatment to individuals for whom previously the door had been closed. Age limits have been relaxed, old cerebral-vascular[12, 13] accidents, coronary thrombosis, and cardiomegaly are no longer considered contraindications.

A compensated heart, acceptable kidney function as demonstrated by intravenous pyelography, a nonprotein nitrogen below 45 mg. per 100 cc. of blood, urea clearance of 60 per cent or greater, and concentrating ability to at least 1.014 are absolutely essential.[12]

We do not believe that suspected generalized arteriosclerosis is a definite contraindication[11] to surgical treatment since the operative results in a single case cannot be predicted with certainty.[14, 15] Each case must be judged upon its merits in so far as the chronological status versus the physiological status is concerned.

No accurate prediction of the results of sympathectomy can be made from the findings of preoperative tests for lability of the vascular bed (cold pressor test,[16] amytal test, other sedation and bed rest, or with tetra-ethyl-ammonium in our own laboratory[17]). In a good percentage of cases postoperative results will follow in harmony but too frequently

they seem to bear an inverse relationship to preoperative calculations based upon these tests.[18]

Age.—During the earlier phase of our experience with the surgical treatment of hypertension a more or less arbitrary upper age limit of forty-five years was set. The reason for this limitation was the belief that sclerosing changes in the arteriolar bed would be so fixed as to render irreversible any change in vascular capacity hoped for with sympathectomy. This is not altogether the case since fixed arteriolar change may be seen in any age group.

There is no question but that generalized sclerosing changes limit the possibility of a good response to sympathectomy; however, there is no way of determining the degree or extent of such a process in any one individual, particularly in the renal and splanchnic vascular beds, by any of our present gross methods. For this reason, patients having generalized evidence of sclerotic change are not denied surgical treatment and a significant number have shown a satisfactory response to the procedure.

Many persons are physiologically younger than their chronological age would indicate and many have had their hypertension for only a relatively short time, thus minimizing the chance of fixed vascular change. Several of our patients have been in the age group of 50 to 55. The oldest patient operated upon was 63 and the youngest 8.[13]

Heart Disease.—In a group of 384 patients selected from Peet's series having hypertensive or coronary heart disease shown objectively by significant orthodiagram and electrocardiogram changes preoperatively, 50 per cent were living five to twelve years after operation.[19] Of the survivors 93 per cent have normal hearts by all subjective and objective criteria. Forty-one per cent of those showing abnormal preoperative electrocardiograms now show normal to significantly improved tracings. Forty-four per cent of the survivors with preoperative cardiomegaly showed normal heart size maintained five to twelve years postoperatively.

Of those patients having coronary occlusive heart disease prior to operation eight out of eleven were surviving five to nine years after operation.

Many patients are reluctant to consider what to them seems a drastic therapeutic measure until they have become cardiac cripples, having experienced decompensation, coronary occlusion, or suffered from severe and repeated anginal seizures. It has been shown that, as a group, even in the light of the above statistics, these individuals have a poorer over-all prognosis than those cases in which there have been no complicating cardiac factors.[12] Attempted salvage is, however, justified.

However, heart disease is not a contraindication to surgical treatment. It has been our experience that a time interval of six to twelve months following an occlusive accident is optimal for election of

surgical treatment.[19] Any time following compensation by digitalization of a decompensated heart per se may be elected for operation.

Malignant Hypertension.—The term "malignant" has become synonymous with the word "terminal" from a practical, clinical point of view. One or all phases of the ultimate evidence of severe damage to the organism are evident: marked encephalopathy (psychoses, convulsions, profound headache, coma); severe retinopathy with edema of the nerve heads and/or the retinal layers; hemorrhages and exudates; profound cardiac failure; or renal insufficiency.

It is true that occasionally one may interview a patient and from the subjective history and objective residuals deduce that he must have had a "malignant" episode in his hypertensive career. Such hypertensive "storms" or transitory "malignant" episodes do occur and for some reason subside spontaneously. This, however, is the exception to the rule.

Papilledema is the definitive finding evidencing the "malignant" phase of the hypertensive state.[15, 20] The operative mortality in Peet's series in those patients without papilledema is 1.6 per cent as compared to an operative mortality of 10 per cent in those cases having grade IV (KWC) funduscopic changes (malignant hypertension.)

Of 143 patients with malignant hypertension operated upon in our series, 21.6 per cent have survived five to eleven years since operation. This is remarkable when compared to survival rates for the malignant phase of arterial hypertension managed by other methods.

If splanchnicectomy is performed before evidence of cardiac strain is manifest, the prognosis for malignant hypertension treated surgically is good.[21] If gross cardiac disease exists, the prognosis for more than a two years survival is poor.[12]

Similarly, in cases of malignant hypertension with evidence of kidney damage of significant functional degree, surgical treatment is only palliative. None of our series in the group of patients with malignant hypertension having a nonprotein nitrogen above 45 mg. per 100 cc. of blood survived more than two years following operation.

Cerebral Vascular Disease.—Formerly in our clinic an individual with clinically evident cerebral vascular disease was denied the possible benefits of surgery. In an effort to prevent further damage it is now believed that these patients are entitled to surgical treatment, but that each case must be judged individually.[13]

Five to eleven years postoperatively, forty-eight of a total of seventy-three patients operated upon after cerebral vascular accidents were still living and, of these, forty-three have had no further difficulty. Most of the deaths were in the group suffering from malignant hypertension.[12] It therefore seems worthwhile to perform a splanchnicectomy in some patients who have had a cerebral vascular accident with reasonable hopes of preventing another stroke. Of course the operative

risk is greater, since in this group, as in the group having had previous coronary infarction, the possibility of further thrombosis is greatly increased with the sudden fall in pressure during the procedure.

Kidney Disease.—In a five to eleven year follow-up study of 117 patients, Peet and Isberg found that of fifty patients who had impaired kidney function prior to operation 36.4 per cent showed significant improvement in concentrating ability, 52.6 per cent were unchanged and only 11 per cent were worse.[12] This latter group of living patients was asymptomatic in regard to residual hypertensive nephropathy. All of these patients had had kidney damage caused by the hypertension.

Our experience with pyelonephritis has been comparable to that of Smithwick[8], namely, that these patients can be helped.

We have treated a small group of patients by sympathectomy who had undergone nephrectomy for unilateral congenitally small kidneys or unilateral pyelonephritis and contracted kidneys and had had no relief afterwards from their hypertension. The greater percentage of this group has done well and a few have done exceptionally well after a bilateral supradiaphragmatic splanchnicectomy.[22]

Pregnancy.—A significant group of women develop their first manifestations of hypertension during pregnancy. This may be asymptomatic or associated with other toxemic or pre-eclamptic signs and first become recognized when the picture is full blown.

As a rule, these patients show a better response as a group to sympathectomy than women having arterial hypertension per se.[23, 24]

Many of these women are well within the child-bearing age and yearn for children of their own. There is often a history of multiple miscarriages. After splanchnicectomy these patients are followed closely for at least two years particularly with regard to kidney function. If this remains satisfactory (normal concentrating ability, normal urea clearance and nonprotein nitrogen below 45 mg.) and blood pressure levels have remained normal or appreciably lowered, the patient is permitted to risk a pregnancy the course of which is to be followed meticulously by the obstetrician.

We have operated upon a small group (five) of pregnant women who were known hypertensives prior to pregnancy.[25] Owing to the rapid symptomatic progression of their hypertension during this state and since they desired to risk going to term, splanchnicectomy was carried out successfully in all five. None aborted following operation. The blood pressure fell to normal levels in three of this group; in two it did not.

It appears that, if the pregnant hypertensive woman is desirous of carrying her pregnancy to term and is actually threatened with the major complications of her combined status, splanchnicectomy has much to offer. The other alternative is interruption of the pregnancy.

TECHNIC OF SURGICAL TREATMENT

In the search for an effective surgical method of attacking the problem of hypertension several technics have been developed. Those introduced by Peet (1933) and Smithwick (1938) have been most widely used. Peet's series of now more than 1800 cases and Smithwick's series of more than 1200 cases are by far the largest. Poppen and Grimson have large individual groups of cases treated by their methods. Earlier methods have not proved of as great value.

Attempts to analyze end results on a comparable basis in isolated series of cases are not literally practicable, primarily because of the wide variations in blood pressure among hypertensive patients. Such a comparison would be academic at any rate. Basically the over-all results of the various technics are quite comparable and about equally effective. From a practical point of view it would appear that the minimum procedure giving the maximum effect should be the procedure of choice.

Supradiaphragmatic Splanchnicectomy and Lower Dorsal Sympathectomy (Peet).—Peet first performed this operation in 1933 upon a patient suffering from malignant hypertension.[27] The results were dramatic.

Initially, lower dorsal sympathetic ganglia 10–11–12, their rami and the splanchnic nerves were removed.[26, 27] This is accomplished by resection of about 1½ inches of the eleventh rib, approaching extrapleurally the greater splanchnic nerve and thoracic sympathetic ganglionated chain. By tugging cephalad upon the greater splanchnic nerve it is possible to bring the upper pole of the celiac ganglion into view and the nerve is cut at that point.

During the past ten years the procedure has gradually been extended cephalad to include the seventh dorsal sympathetic ganglion. In many cases the sixth ganglion and occasionally the fifth can be reached. The purpose of this extension of the originally limited procedure is to limit the possibility of regeneration of nerves.

We have reoperated upon a few (six) patients having recurrence of hypertension and have searched for regenerated fibers. These patients had all had marked lowering of their blood pressure for periods varying from two to nine years. No grossly visible nerves have been found. However, in tissue resected from the previous location of the chain, microscopic sections demonstrate multiple, fine, thinly myelinated nerve fibers.

In all but two of these patients it was found that the twelfth ganglion had not been removed. In these cases the diaphragm was stripped further caudad and the first lumbar ganglion removed as well.

The Peet procedure is carried out as one operation, both sides being done at the same time. The average operating time is one hour. The patient is discharged from the hospital between the tenth and fourteenth hospital days.

Lumbodorsal Sympathectomy and Splanchnicectomy (Smithwick).—Smithwick developed his present technic in 1938. Recognizing earlier the numerous failures of the subdiaphragmatic procedure,[28] he extended his operation through and above the diaphragm to include the eighth dorsal sympathetic ganglion. The lower limits of the dissection include always lumbar ganglion one—frequently two and three—as well as the lower dorsal chain and the splanchnic nerves. The chief advantage of this exposure, aside from its effect upon the hypertensive state, is that it enables exploration of the adrenal glands and kidneys thus excluding the possibility of a neoplastic (adrenal) etiology for the increase in blood pressure.

Both kidneys are biopsied thus gaining some information of limited prognostic value in each case.

In instances of protracted angina pectoris, Smithwick utilizes total thoracic sympathectomy from the inferior cervical ganglion through the twelfth dorsal ganglion with resection of the available splanchnic nerves within the thorax. Patients suffering unusual tachycardia are subjected to a similar procedure with the exception that the stellate and first thoracic ganglia are not removed.

The operation is carried out in two stages, one side at a time, a week to ten days apart.

Poppen has extended the Smithwick technic cephalad to include the fourth and/or third thoracic sympathetic ganglion. This necessitates a longer incision and resection of the eighth as well as the eleventh rib. He has recently reported his results in 100 consecutive cases in which this technic has been used.[11]

Total Thoracic Sympathectomy, Celiac Ganglionectomy and Splanchnicectomy (Grimson).—Grimson evolved his concept of surgical relief of the hypertensive state from results obtained in the laboratory using dogs as the test animal.[5] The powerful vasopressor stimulus of increased intracranial pressure was utilized for the induction of hypertension in the animals. He found that a reversal of the experimental hypertensive state could be brought about effectively only by total thoracic sympathectomy and supradiaphragmatic splanchnicectomy.[9, 10]

Grimson's operation is performed in two stages a week to ten days apart. The approach to the sympathetic chain and splanchnic nerves is transthoracic, the third and seventh ribs being resected. The dorsal sympathetic chain from the stellate ganglion to the twelfth thoracic and the splanchnic nerves are dissected out and removed as a complete anatomical specimen. This procedure induces a greater degree of postural hypotension which adds considerably to the postoperative morbidity until compensatory adjustment occurs.[30]

Smithwick believes that such an extensive procedure is probably not entirely amenable to the problem of hypertension in humans since individuals failing to respond to his procedure failed as well to respond to total thoracic sympathectomy.[28] He has corroborated Grimson's observations in patients having coronary heart disease, angina pectoris, or unusual tachycardia. However, in our experience with the Peet procedure we have also obtained relief from anginal seizures in many patients.[12]

COMPLICATIONS OF SURGICAL TREATMENT

Mortality.—It must be emphasized that, in any individual suffering from a constitutional disorder having such widespread and devastating effects upon the organism as a whole, the risk associated with any major rectifying procedure has a direct relationship to the time and effect quantities in the equation.

It is therefore remarkable that in all hands of experience the mortality of sympathectomy for hypertension is of minimal degree. The estimated mortality in Peet's series of 1500 cases was 3.2 per cent[12] and in Smithwick's series of 1200 unselected cases the mortality was 1 per cent; in selected cases the rate was a fraction of this figure.[28] The Peet series is made up of a good many patients having malignant hypertension and in older age groups with more advanced changes in the cardiovascular-renal status, which explains the slightly higher mortality rate.

Morbidity.—Postoperative morbidity is chiefly the result of trauma to the intercostal nerves and disturbance of the sympathetic outflow to

the gut. Patients complain of three kinds of pain: aching back pain in the incisional site, pain radiating anteriorly over the course of the lower intercostal nerves, and severe abdominal cramping.

The intercostal pain is primarily paresthetic in nature, a burning tenderness which makes the skin of the abdomen extremely sensitive to touch. There may be an accompanying sense of bloating due to paresis of the abdominal muscles, which lasts a variable length of time but usually disappears completely within three to four months after operation.

The abdominal cramping pain is at times extremely severe. It seems to respond neither to sympathomimetic nor to parasympathomimetic drugs. Occasionally atropine offers some relief. This pain usually comes within forty-eight to sixty-two hours following operation and may last a week to ten days. It may be that it represents compensating activity on the part of the parasympathetics and Auerbach's plexus. However, postoperative x-ray study of the gastrointestinal tract in a series of our patients during this phase has shown contrarily a static picture with dilatation of the small gut and stomach.[31]

Postoperative hypotension is a real factor in the more extensive surgical procedures. This can be controlled by the use of ace bandages to the lower extremities and abdominal binders.

Small tears may occasionally occur in the pleura; as a rule, however, they induce no subjective or objective postoperative effects. With extensive pleural tears subcutaneous emphysema of the neck and upper thorax may result. This air is usually absorbed over a period of two to three days.

Minimal pulmonary atelectasis is probably the simplest and most common postoperative complication and can be recognized early and dealt with effectively. Pleural effusion associated with pulmonary atelectasis is rarely seen to the extent that it requires thoracentesis.

Pneumothorax is watched for closely during the immediate forty-eight hour postoperative period but is rarely seen. If present it is treated by thoracentesis. This is not a tension pneumothorax but results from a fault in closure of the chest wound.

Vascular Accidents.—The operation and the acute postoperative period may be complicated by coronary thrombosis and cerebral and/or pontine thromboses. This possibility is always anticipated and for this reason the blood pressure is followed minute by minute during the procedure and is not allowed to fall below a level decided upon before anesthesia is induced. Even so, deaths from this cause are mainly responsible for the operative mortality.

We have had four cases of thrombosis of the anterior spinal artery with resultant permanent residual ischemic myelitis.

Chylothorax.—The thoracic duct is anatomically intimately related to the splanchnic nerves as they pass through the diaphragmatic hiatus on the right side. There are also radicles of the chylous drainage sys-

tem criss-crossing the vertebral bodies anteriorly. Some of these are large.

We have had five patients with postoperative chylothorax. All were treated expectantly with repeated thoracenteses, and the effusion was controlled in all but two. Of these two one expired of coronary occlusion when the chest was reopened to clip the duct and in the other the chylothorax was successfully controlled by finding the torn duct and applying silver clips.[32] None of these patients exhibited the expected cachexia associated with loss of chyle.

Sterility in Males.—Theoretically the effective stimulus for contraction of the seminal vesicles is mediated through lumbar ganglia one and two. With removal of these ganglia one might expect inadequate numbers of sperm in the ejaculum thereby inducing sterility.

This is not a reliable deduction since pregnancy has been known to occur in the consorts of upper lumbar sympathectomized males thought to be sterile for the above reason. Furthermore, it is reasonable to assume that even with loss of contractility of the seminal vesicles, sufficient overflow would be constantly present thus rendering permanent sterility improbable.

SUMMARY

Sympathectomy in all experienced hands has proved an extremely useful adjunct to a medical therapeutic armamentarium in hypertension which for over-all practical purposes has been significantly ineffective. This is particularly true of the malignant phase of arterial hypertension.

Surgical treatment of the hypertensive state is not a specific therapeutic method nor a cure. However, to date, it has proved to be the most effective method of management. It is an attack upon a significant sector of the vicious neurohumeral cycle of events that has been touched off by some as yet nebulous factor. The results are effective.

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PRECORDIAL LEADS IN CLINICAL ELECTROCARDIOGRAPHY

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The introduction of precordial leads represents the single most important recent advance in augmenting the diagnostic utility of the electrocardiogram. In less than two decades the value of these leads has been universally accepted by experienced cardiologists, so that at present an electrocardiographic examination which does not include precordial leads must be considered incomplete. Although it is true that there are still a number of unsolved problems concerning the theory and interpretation of the precordial electrocardiogram, sufficient experience has been gained in its use so that its specific advantages may be clearly stated. It is the purpose of this report to discuss and illustrate these advantages as we have learned them in the course of an extensive experience. Highly theoretical and controversial considerations will be omitted for the most part, in order to preserve the practical nature of the review.

THE NATURE OF PRECORDIAL LEADS. THE LOCATION OF THE INDIFFERENT ELECTRODE

A precordial lead records, as faithfully as is possible in the living human subject, the electrical changes occurring at the epicardial surface of that portion of the heart subjacent to the chest electrode. It is the closest approach we have to obtain direct epicardial leads from the surface of the heart, and it was in an attempt to reproduce the electrogram of animals that the precordial leads were introduced in human electrocardiography. A precordial lead differs from a standard lead in that in the case of the latter the two electrodes are at a relatively great and an approximately equal distance from the heart, and the electrical changes occurring at each of the electrodes exert a more or less equal influence in determining the form of the final record. As a consequence, such a record represents the algebraic difference between the potential variations of two electrodes of approximately equal influence. The principal practical disadvantages of such leads are, first, conspicuous changes may occur which do not reflect intrinsic cardiac abnormalities, but rather variations in the posi-

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tion of the heart in the thoracic cage; second, the direction of a given deflection does not necessarily indicate the true polarity recorded at that instant; third, the relatively great distance of the electrodes from the heart does not permit accurate localization of disease within the heart. In a precordial lead, however, the close proximity of one electrode to the heart enables the final record to be a fairly accurate representation of the changes occurring at the heart's surface since the magnitude of these changes is much greater than at distant points on the extremities. In a precordial lead, therefore, the distant electrode exerts relatively little effect on the tracing. Furthermore, the use of an exploring electrode over the precordium facilitates detection of some cardiac abnormalities which are beyond the range of the fixed standard limb leads.

There is no unanimity of opinion as to the most desirable location for the "indifferent" electrode. The reports of the American and British Heart Associations[1] recommended that this electrode be placed on the right or left arm or the left leg, or that it be connected to a central terminal formed by leading wires from electrodes on each of the three extremities to a common terminal, a resistance of 5000 ohms being interposed between each extremity and the terminal. It is our practice to pair the precordial electrode with one on the left leg. It is necessary to point out that the precordial electrocardiogram varies somewhat, depending on the location of the indifferent electrode. It is beyond the scope of this paper to discuss the problem in detail. The variations are of relatively little significance in the majority of cases. Occasionally, however, the electrical changes occurring at the extremity electrode produce sufficient distortion of the tracing to lead to incorrect diagnosis. For example, in a normal male subject with an asthenic habitus, the QRS complexes in leads CF_4 and CF_5 were inverted. This abnormality in a subject with right axis shift suggested possible right ventricular preponderance. When the central terminal was used as the indifferent electrode the QRS complexes in V_4 and V_5 were normal. The central terminal in this case obviated the distortion produced by the potential variations of the extremity electrode.

THE SELECTION OF PRECORDIAL POSITIONS

As in the case of the location of the "indifferent" electrode, there is a difference of opinion as to the number and location of precordial positions to be used in recording precordial leads. It is, however, inherent in the principle of an exploring electrode that several precordial positions be used. All experienced electrocardiographers are now in agreement on this point. Unfortunately, many physicians still take only one chest lead, from the cardiac apex. *This practice is to be discouraged.* Frequently this lead is perfectly normal, whereas if the chest electrode is moved a few centimeters away from the apex in any direction,

striking abnormalities may be detected. Furthermore, the electrocardiographic diagnosis of some abnormalities is based on the demonstration of a pattern of changes in leads over the right side of the precordium, left side of the precordium and the transition zone between the two. Such patterns cannot be obtained when only one lead is taken. Routinely, we employ three chest positions; C_2 (the fourth intercoastal space just to the left of the sternum), C_4 (the junction of the left midclavicular line and the fifth intercoastal space), C_5 (the left anterior axillary line at the same horizontal level as C_4). In certain cases additional positions are used (the left mid and posterior axillary lines at the level of C_4, the right fourth parasternal intercoastal space, or points in the second or third left intercoastal spaces in the mid axilla). These are of particular value in detecting small, well localized areas of myocardial infarction when the routine leads are normal or equivocal. The mobility of the precordial electrode is one of its main advantages, and it should be exploited. In the following pages discussion will be limited to the routine precordial leads we use, CF_2, CF_4 and CF_5.

THE PRECORDIAL ELECTROCARDIOGRAM OF THE NORMAL SUBJECT

The QRS complexes in the chest leads of a normal adult show a consistent pattern as the exploring electrode is moved from right to left. The R wave is small and narrow in CF_2 and becomes taller and broader in CF_4 and CF_5. The S wave is deep and broad in CF_2 and becomes smaller and narrower in CF_4 and CF_5. Thus, the R-S ratio increases as the exploring electrode is moved from right to left. This pattern is fairly constant irrespective of shifts in the direction of the electrical axis as found in the limb leads except when these are marked. Figure 47, *A*, shows normal right axis shift. Figure 47, *B*, shows normal left axis shift. The chest leads are essentially the same in both records. The P wave may be upright or small and inverted, and the T wave is upright except in a rare young adult who may have an inverted T wave in CF_2 and even more rarely in CF_4. The S-T segment is isoelectric or slightly elevated. It is important to recognize that in infants and young children the T waves in CF_2 and CF_4 are normally inverted (Fig. 47, *C*). In older children and adolescents the T wave in CF_2 only is normally inverted or notched.

The criteria for the diagnosis of normal and abnormal deflections in the chest leads are given in detail elsewhere.[2] However, certain points should be emphasized. The absence of an R wave in CF_2, CF_4 or CF_5 is abnormal. The absence of an S wave in CF_2 is abnormal. The presence of a Q wave in CF_2 is abnormal. A deep Q wave in any chest lead is abnormal. An inverted T wave in any chest lead is abnormal except in children and young adults as mentioned above. A depressed S-T segment in any chest lead is abnormal except for slight depression in CF_5.

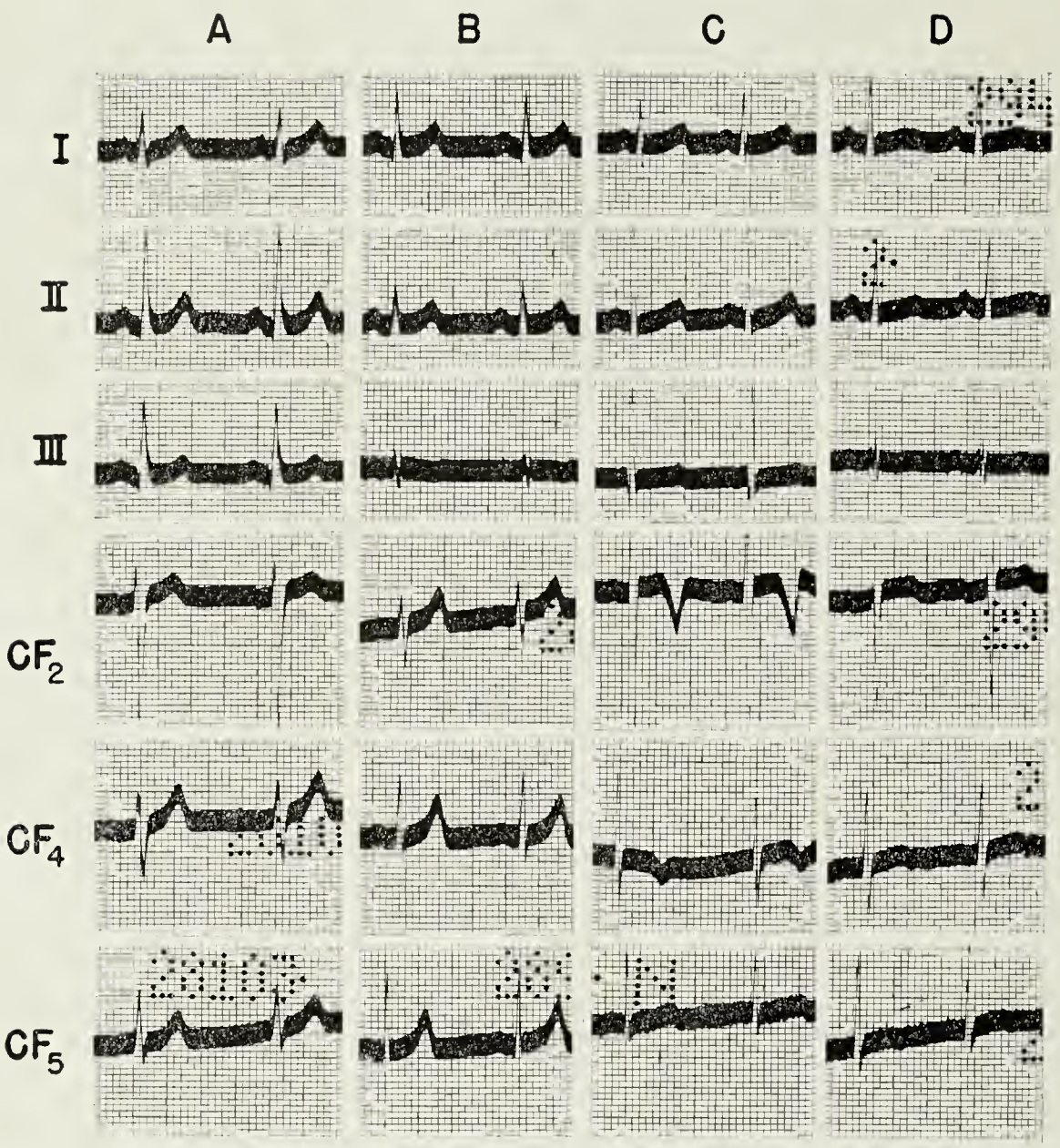

Fig. 47.—Examples of normal electrocardiograms (*A, B, C*) and nonspecific precordial lead abnormalities (*D*). (Discussed in text.)

MYOCARDIAL INFARCTION

Although in most instances the standard limb leads provide clear evidence of myocardial infarction, not infrequently they are equivocal or actually normal. In such cases the precordial leads may show the diagnostic changes. These changes may be present in all of the chest leads or in only one or two of them. At times the limb leads show a pattern of abnormalities which is difficult to distinguish from heart strain whereas precordial derivations are indicative of recent or healed infarction. The chest leads may be used to locate infarcts more or less precisely and to indicate the extent of the infarct. In acute cor pulmonale due to massive pulmonary embolism or in acute diffuse pericarditis the limb leads may resemble posterior or anterior wall infarction respectively, whereas the chest leads help to establish the correct diagnosis.

The electrocardiogram reproduced in Figure 48, *A*, is an example of an extensive recent anterior wall infarct showing the classical changes in both standard and precordial leads. In lead 1 there is a relatively deep Q wave and a small R wave. The S-T segment is abnormally

elevated and takes origin close to the summit of the R wave. The T wave is small and inverted. Deep S waves are present in leads 2 and 3, and the S-T segment is elevated in lead 2 and depressed in lead 3. The diagnostic changes are magnified in the precordial leads. All of them show the disappearance of the R deflection for which has been substituted a deep QS wave. The S-T segment is markedly elevated, indicative of currents of injury, and the T wave is small and diphasic in CF_2 and inverted in CF_4 and CF_5. In view of the fact that all the precordial leads show the changes of recent myocardial infarction it may be inferred that the infarct is extensive, involving regions of the

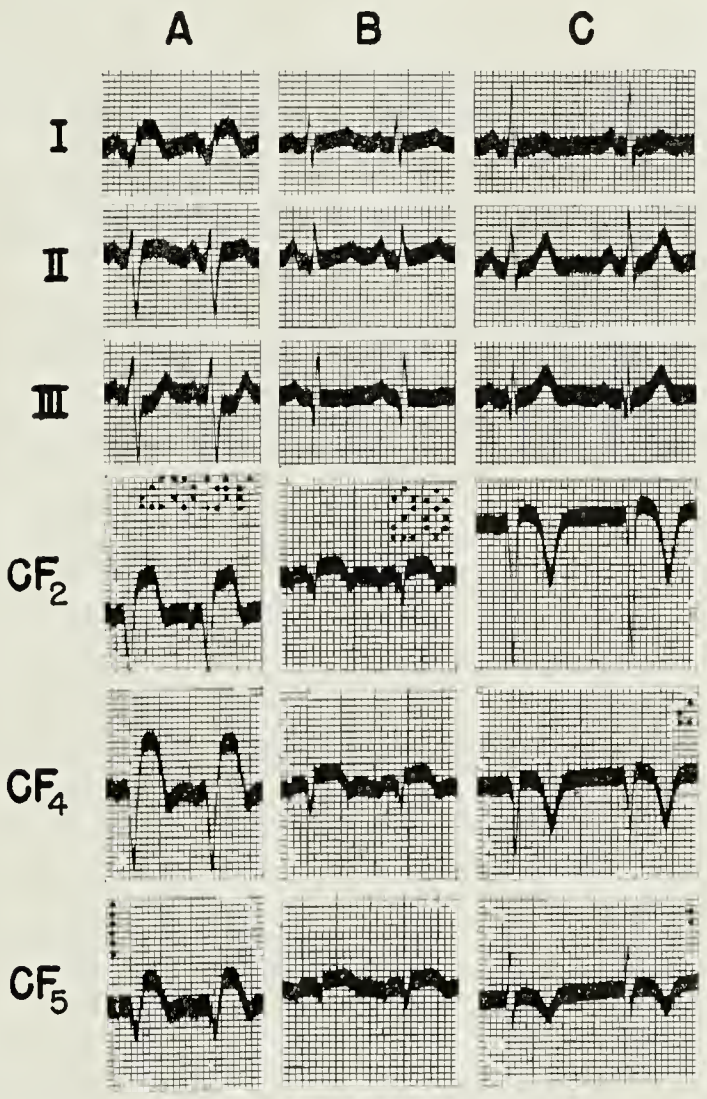

Fig. 48.—Examples of anterior wall infarction. (Discussed in text.)

myocardium close to the interventricular septum (CF_2) and the more lateral left ventricular wall (CF_5) as well as the myocardium intermediate between these two positions (CF_4).

In Figure 48, *B* and *C*, the electrocardiograms illustrate the diagnostic value of the chest leads in recent and healed infarctions when the standard leads are equivocal or normal. In Figure 48, *B*, the changes indicative of recent anterior wall infarction are clear in the chest leads, particularly CF_2 and CF_4 (absence of the R wave and presence of a QS wave in CF_2, deep Q wave in CF_4, elevated S-T segments in all chest leads and inverted T waves in CF_2 and CF_4). The limb leads, however, show only a tendency to low voltage, small

Q waves in leads 2 and 3 and slight depression of the S-T segment in lead 3. The limb leads, therefore, are not diagnostic of anterior wall infarction. In healing or healed anterior wall infarction the superiority of the chest leads may be even more striking than in recent infarction, as is shown in Figure 48, *C*. Here, the limb leads are abnormal because T_1 is smaller than T_3, but this is not diagnostic of remote anterior wall infarction. The precordial leads, however, show a deep QS deflection in CF_2 and CF_4 and inverted T waves in all the chest leads, most marked in CF_2 and CF_4. These changes are diagnostic of a healing or healed anterior wall infarction.

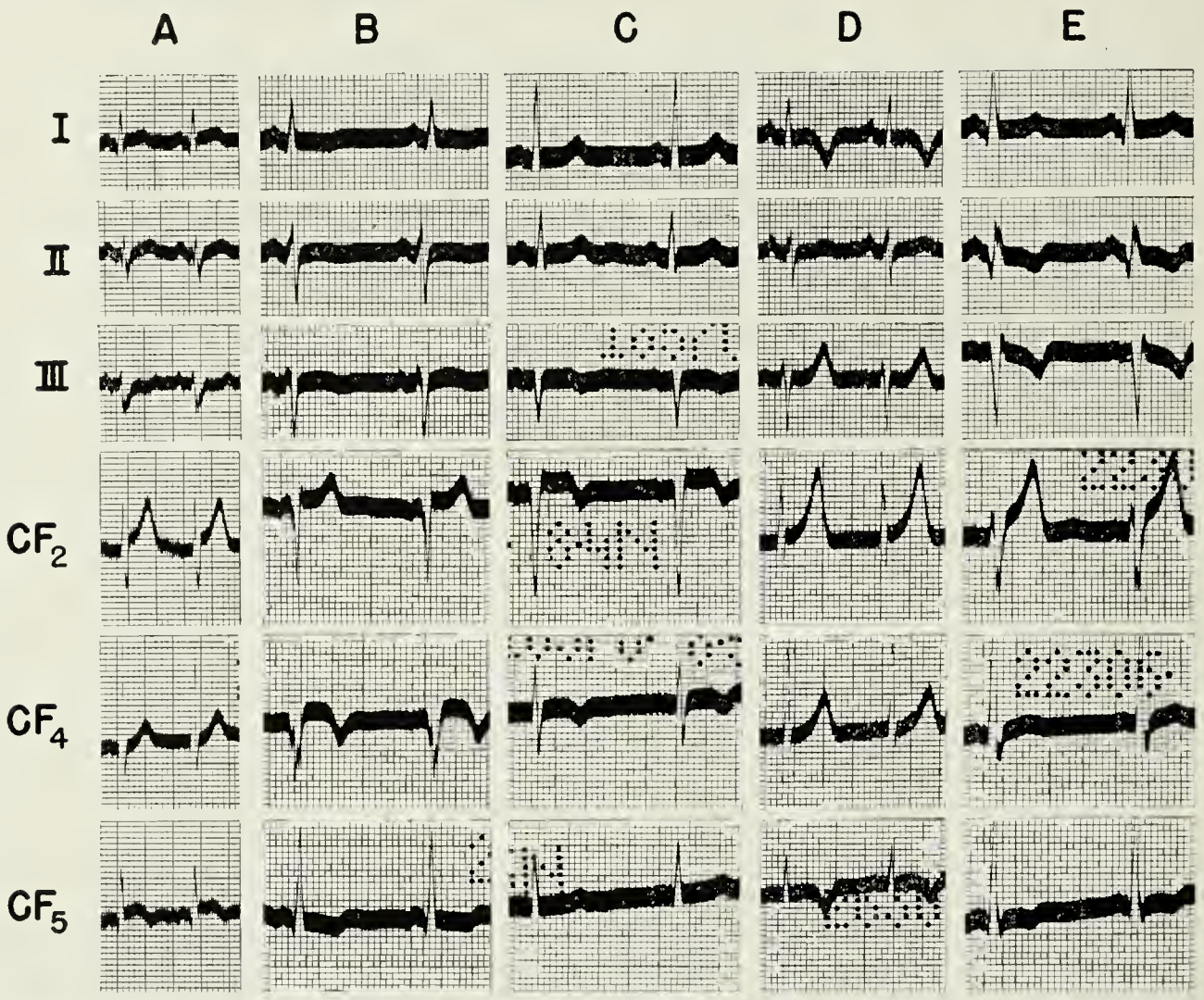

Fig. 49. Examples of anterior wall infarction (*A*, *B*, *C*), anterolateral infarction (*D*) and posterolateral infarction (*E*). (Discussed in text.)

Inasmuch as precordial leads record principally (but not exclusively) the electrical changes occurring at the epicardial surface of that portion of the heart subjacent to the chest electrode, they are capable of detecting well localized areas of injury or disease. If the diseased zone is small enough, the diagnostic changes will appear in only one of the precordial positions. If it is more diffuse, more than one position will record the changes, but these will be most pronounced in the position closest to the area of disease. Figure 49, *A*, is the electrocardiogram of a patient with a recent myocardial infarction. The limb leads suggest this diagnosis by virtue of the elevation of the S-T segment in lead 1 and the depression of the S-T segment in lead 3. The changes in the chest leads are limited exclusively to CF_5 which

shows an abnormally elevated S-T segment and inverted T wave (and a small Q wave). The infarct, therefore, is located in the more lateral portion of the left ventricular myocardium since position C_5 records especially well potential variations from this region of the heart. In this case lead CF_5 is more diagnostic of infarction than the limb leads. It is apparent, then, that the valuable confirmatory information afforded by this precordial lead would not have been obtained had only lead CF_4 been recorded. In the electrocardiogram shown in Figure 49, *B*, although the limb leads and leads CF_2 and CF_5 are abnormal, they are not diagnostic of myocardial infarction. CF_4, however, is typical, showing the large notched QS deflection, the elevated S-T segment and the deeply inverted T wave. Only in this lead are the diagnostic changes present. The electrocardiogram shown in Figure 49, *C*, was taken on a patient with a healed myocardial infarct. T wave inversions are present in leads CF_2 and CF_4, but the changes are more characteristic in the former which has abnormalities in the initial ventricular deflection (absence of R wave and presence of QS wave) as well as T inversion. Note that the limb leads are within normal limits. These three examples serve to illustrate the fact that diagnostic changes may appear only in certain precordial leads. It cannot be emphasized too strongly that at least three chest leads should be used in routine electrocardiography. Occasionally it may be necessary to explore the precordium still further in order to detect focal areas of myocardial disease.

The majority of infarcts are neither strictly anterior nor posterior but involve the left lateral wall to some degree. The precordial leads are helpful in diagnosing the lateral wall component of the infarct. In the electrocardiogram reproduced in Figure 49, *D*, the deeply inverted symmetrical T wave in lead 1 and the tall symmetrical T wave in lead 3 are diagnostic of healing anterior wall infarction (confirmatory is the small R in lead 1 and the deep S in leads 2 and 3). The chest leads, however, localize the infarct more precisely to the anterolateral wall, since lead CF_5 alone shows the T wave inversion. The very tall upright T wave in CF_2 is abnormal and confirms the diagnosis of lateral wall involvement. The opposite changes in the T waves in leads CF_2 and CF_5 are predictable on theoretical grounds, but the explanation is beyond the scope of this review. Posterolateral wall infarcts may similarly be diagnosed. In Figure 49, *E*, the presence of deep Q and inverted T waves in leads 2 and 3 is indicative of remote posterior wall infarction. The T wave inversion in lead CF_5 demonstrates the specific involvement of the lateral wall.

Not infrequently it is difficult to distinguish between infarction and heart strain on the basis of limb leads alone. Chest leads are particularly helpful in making this differentiation. The electrocardiogram in Figure 50, *A*, shows limb lead changes suggestive of left ventricular strain ($S\text{-}T_1$ depressed, T_1 inverted, deep S_3). The chest leads, how-

ever, show the characteristic pattern of an extensive anterior wall infarction. It may be that both heart strain and infarction were present simultaneously, but were the limb leads the only leads recorded the diagnosis of recent myocardial infarction would have been missed. The electrocardiogram in Figure 50, *B*, illustrates the same phenomenon except that the precordial leads indicate a healed infarct.

In some cases of myocardial infarction both anterior and posterior walls are involved as a result of a single or several episodes. The true extent of infarction may not be appreciated without the assistance of

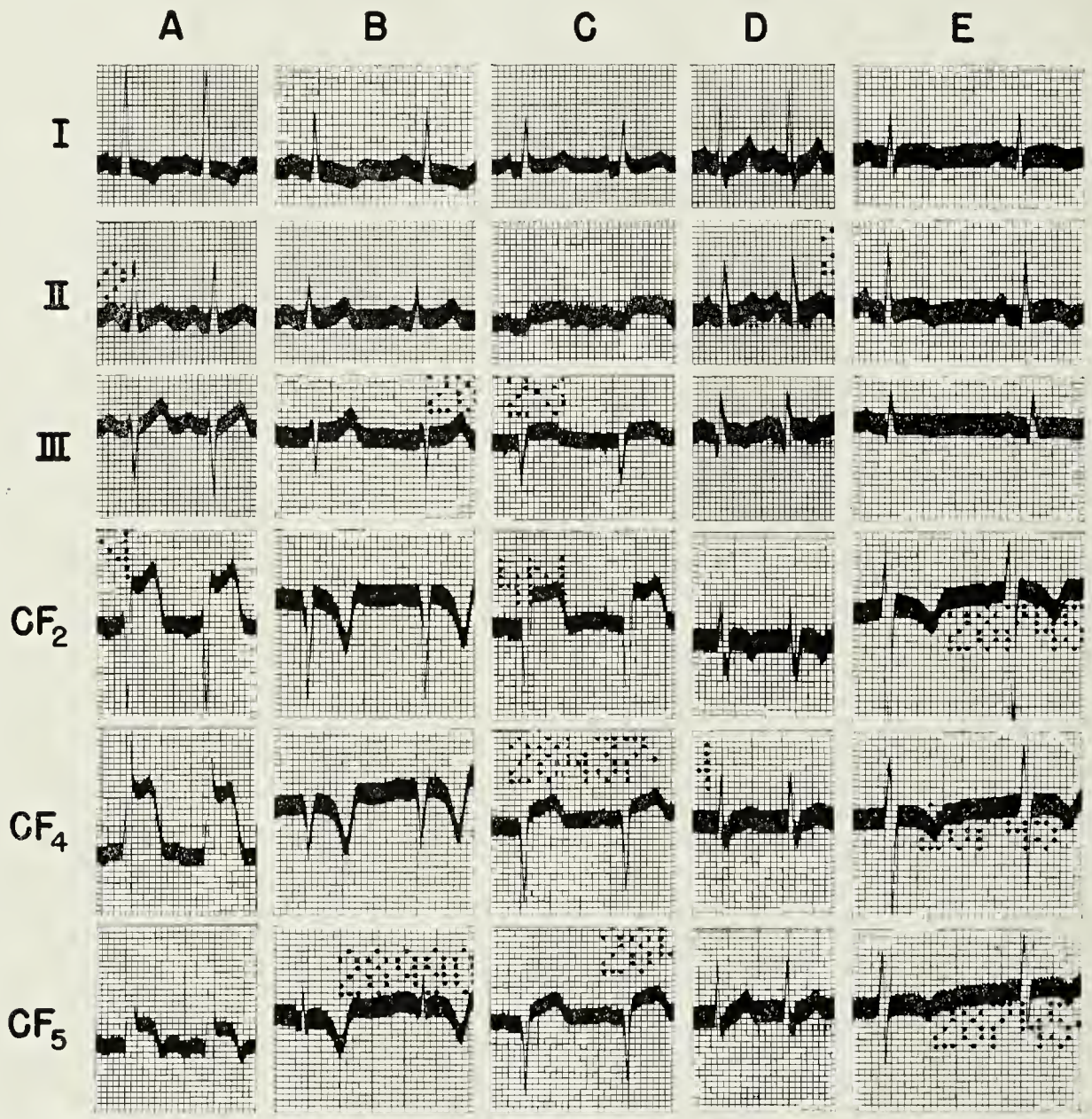

Fig. 50.—Examples of anterior wall infarction (*A, B, C*), acute cor pulmonale (*D*), and diffuse pericarditis (*E*). (Discussed in text.)

chest leads. The electrocardiogram in Figure 50, *C*, shows limb lead changes indicative of recent posterior wall infarction (elevation of S-T segments in leads 2 and 3 and deep QS_2 and QS_3). The precordial leads demonstrate the anterior wall component by virtue of the absence of the R waves (the presence of QS waves) and the elevation of the S-T segments.

Precordial leads are less helpful in the diagnosis of posterior wall infarction than anterior wall infarction because of the lack of changes in the QRS complex. In recent posterior infarction the precordial leads

tend to show depression of the S-T segments. In healing or healed posterior wall infarction the upright T waves in the chest leads become abnormally tall and symmetrical. Occasionally this may be the only precordial residue of a remote posterior wall infarct. Esophageal leads or leads from the posterior thorax may present the diagnostic changes of posterior wall infarction when anterior chest leads are normal. In general, the standard limb leads are more useful than the routine precordial leads in demonstrating posterior wall infarct, but in about 5 per cent of cases, the S-T depressions in the chest leads may be the only early evidence of posterior wall infarction. In selected cases the special leads mentioned above should be used.

In recent myocardial infarction and in healing myocardial infarction, of course, recourse may be had to serial records repeated a few days or weeks apart to make the diagnosis. In old healed infarction when the records are stabilized, seriatim records will not help and contour will be the sole criterion. It is here that the chest leads are so valuable.

ACUTE COR PULMONALE AND PERICARDITIS

Acute cor pulmonale due to pulmonary embolism produces characteristic changes in both standard and chest leads. In acute cor pulmonale (Fig. 50, *D*) the limb leads show an S wave in lead I, a Q wave in lead 3, S-T depression in lead 1 or leads 1 and 2 with the "staircase" ascent. The diagnostic feature of the precordial leads is the inversion of the T wave in lead CF_2 without deviation of the S-T segment, and there may be S-T depression in CF_4 or CF_4 and CF_5 with "staircase" ascent.

In acute diffuse pericarditis (Fig. 50, *E*) there is slight elevation of the S-T segment with inverted T waves in two or all three limb leads. The T wave inversion becomes more pronounced during the healing process, and the S-T segment deviation disappears. Chest leads show T wave inversion. The absence of QRS changes in both limb and chest leads distinguishes acute diffuse pericarditis from myocardial infarction. Similarly, the absence of abnormalities in the initial ventricular deflection may serve to differentiate acute nephritis, hyperthyroidism and other diseases which produce "coronary" T waves from infarction.

HEART STRAIN

The precordial leads are of special value in the diagnosis of heart strain, particularly left heart strain.[3] It is imperative that multiple chest leads be taken since the diagnosis of right or left heart strain is often dependent on a pattern of changes in leads over the right and left sides of the precordium. Lead CF_4 is the least useful of the chest leads in diagnosing these abnormalities in the presence of cardiac enlargement. In left ventricular hypertrophy the precordial leads may show the diagnostic changes when the limb leads are normal or equivocal. In some cases with marked cardiac enlargement a lead from

position C_6 or C_7 rather than C_5 will reveal the changes of left ventricular strain. Furthermore, the chest leads may indicate left ventricular preponderance whereas the limb leads suggest right ventricular preponderance, thus permitting the diagnosis of combined heart strain. In typical left ventricular strain lead CF_2 shows a small R wave, an elevated S-T segment with downward bowing and an upright T wave. CF_5 shows a tall R wave with depression and upward bowing of the

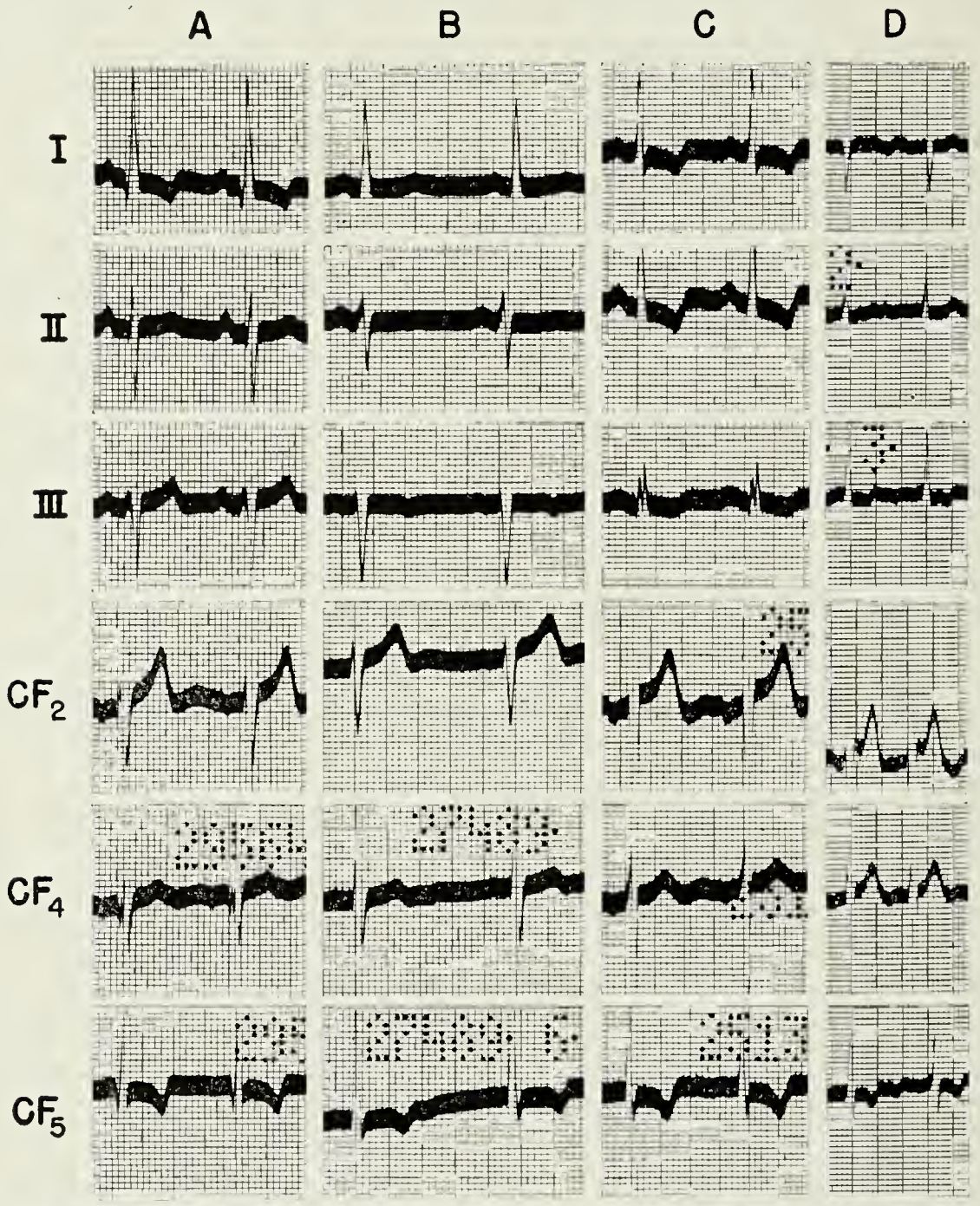

Fig. 51.—Examples of left heart strain (*A, B, C*), and combined heart strain (*D*). (Discussed in text.)

S-T segment and an inverted T wave. Lead CF_4 may be normal or may resemble CF_2 or CF_5, usually the latter. The precordial leads are of less value in the diagnosis of right ventricular preponderance than left ventricular preponderance. The diagnostic pattern, which unfortunately occurs infrequently, consists of relatively tall R waves and small S waves in leads over the right side of the precordium and the reverse in leads over the left side. Thus, the R-S ratio decreases as the exploring electrode is moved from right to left. Inversion of the T wave in CF_2 may also be present in the typical case of the right ventricular

strain. More frequently, the chest leads show mainly downward QRS complexes with small R and deep S waves. Since the latter may be found in CF leads in some individuals with normal right axis shift, this chest lead pattern does not have diagnostic specificity. Occasionally it is necessary to take leads from position C_1 or even from more lateral positions on the right anterior chest in order to demonstrate the tall R waves.

In Figure 51, *A*, a classical six lead pattern of left heart strain is seen. In Figure 51, *B*, the limb leads show deep S waves in leads 2 and 3, a small T_1 and a tiny notched T_2. These abnormalities are not specific, and although one might suspect left ventricular strain from the limb lead pattern this diagnosis would be equivocal. Lead CF_5, however, gives clear evidence of left ventricular strain. The S-T segment is depressed, bowed upward, and the T wave is inverted. The R wave is tall in CF_5 and small in CF_2. Without precordial leads, or with lead CF_4 only, the diagnosis of left ventricular hypertrophy would be speculative rather than definite.

We[4] have used the term "concordant left ventricular strain" to describe an electrocardiographic pattern consisting of upright QRS complexes in the limb leads associated with the S-T-T changes of left heart strain in lead 1 or leads 1 and 2. Precordial leads show classical left ventricular strain. It is important to recognize this variety of left heart strain and not to be misled by the absence of abnormalities in the direction of the electrical axis. The precordial leads provide unmistakable evidence of left ventricular strain even though "left axis deviation" is not present. An example of concordant left ventricular strain is shown in Figure 51, *C*. Note that the heart strain patterns as described above are present in both CF_2 and CF_5 and CF_4 is normal. Valuable diagnostic information would have been missed if only chest lead CF_4 were recorded.

The electrocardiogram shown in Figure 51, *D*, is an example of combined heart strain. The limb leads demonstrate right heart strain since QRS in lead 1 is inverted, the S-T segments in leads 2 and 3 are depressed and the T wave in lead 3 is inverted. The chest leads show left ventricular strain. Note that CF_4 resembles CF_2. Coarse auricular fibrillation is also present. The diagnosis of combined heart strain may be suspected when the chest leads show left heart strain and the limb leads right axis shift without changes in S-T-T configuration. This type is generally seen in younger individuals with rheumatic heart disease. It has been suggested that this pattern represents left ventricular strain in individuals with a vertically placed heart. We prefer to consider such electrocardiograms as examples of combined heart strain (as shown in several necropsied cases), although an exact differentiation is admittedly difficult. Occasionally one sees typical left heart strain in CF_4 or CF_5, but CF_2 has a relatively tall R wave. Such electrocardiograms may also be indicative of combined heart strain.

INTRAVENTRICULAR BLOCK

The diagnosis of intraventricular block can be made satisfactorily from the limb leads alone, since the only criteria for its diagnosis are a QRS interval which has a duration of 0.12 sec. or more and a normal P-R interval. The earliest use of precordial leads concerned attempts to localize the block more accurately (to the right or left bundle branches). The absolute validity of this electrocardiographic differentiation is still subject to some difference of opinion among electrocardiographers. Pathologic and physiologic studies from several labora-

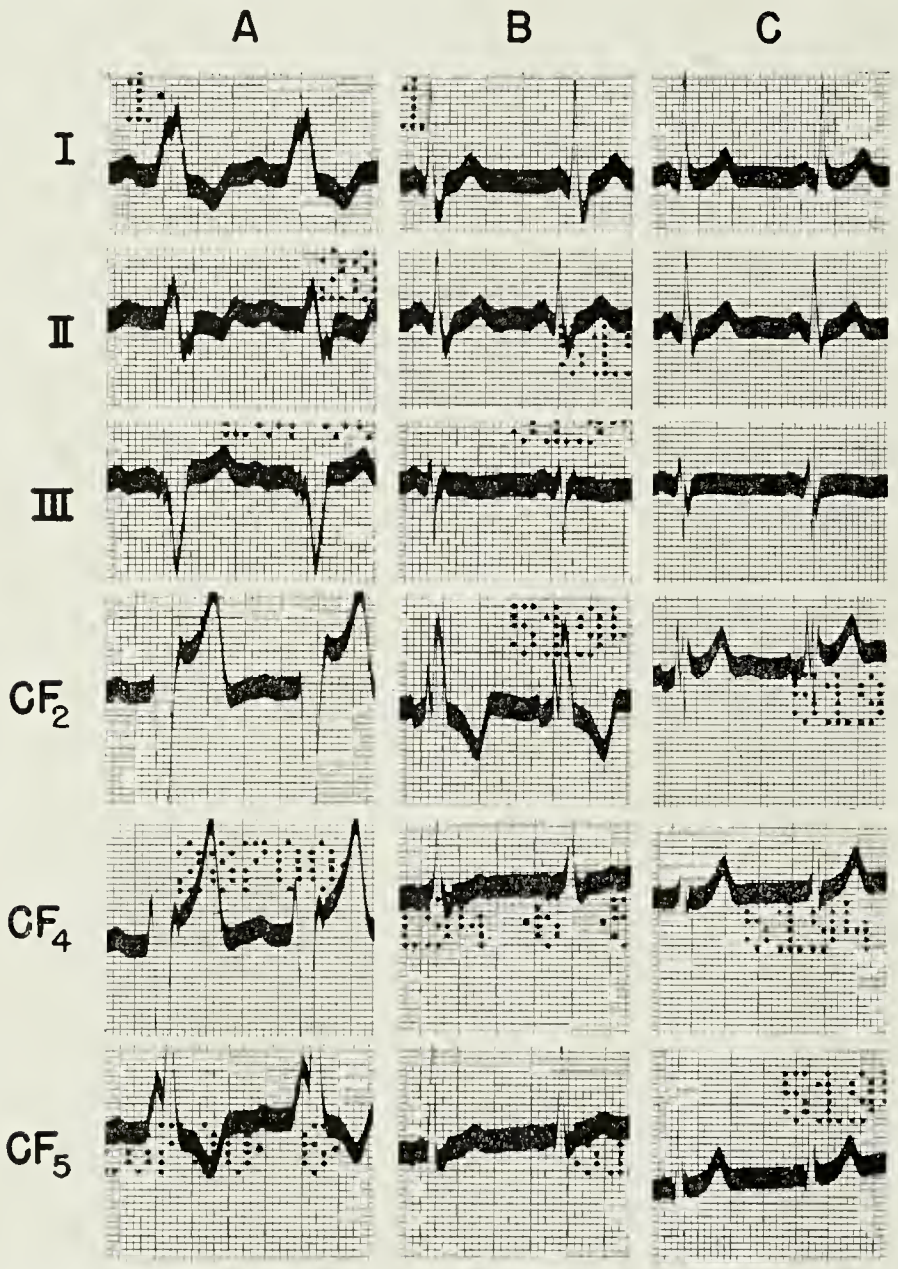

Fig. 52.—Examples of intraventricular block. (Discussed in text.)

tories indicate that although in the majority of cases it is possible to correlate lesions in the bundle branches or delay in activation of one ventricle with a specific type of electrocardiographic abnormality, it is not always possible to do so. In order to avoid a terminology which implies greater precision than is justified by the evidence, we use purely descriptive expressions based on electrocardiographic patterns. Hence, we recognize intraventricular block of the common type (which usually corresponds to block of the left bundle branch system), intraventricular block of the S and uncommon types (which

usually correspond to block of the right bundle branch system) and intraventricular block of the indeterminate type.

An example of typical intraventricular block of the common type is shown in Figure 52, *A*. The QRS duration is 0.20 sec. There is no S wave in lead 1. The QRS deflections are oppositely directed in leads 1 and 3, and the S-T segments and T waves in the limb leads are deviated in directions opposite to the initial ventricular deflections. In CF_2 the R wave is small, the S wave broad and deep, the S-T segment elevated and the T wave upright. In CF_5 the R wave is broad and notched, the S-T segment depressed and the T wave inverted. CF_4 resembles CF_2. No Q waves are present in leads 1 or CF_5. First degree auriculoventricular block (P-R 0.24 sec.) is also present in this example. The electrocardiogram in Figure 52, *B*, illustrates intraventricular block of the S type. The QRS duration is 0.13 sec., and there is a broad S wave in lead 1 and lead 2. In CF_2 the R wave is tall, broad, splintered and notched, the S-T segment is depressed and the T wave is inverted. Broad S waves are present in leads CF_4 and CF_5.

Occasionally a chest lead may demonstrate intraventricular block before this appears in limb leads. The electrocardiogram in Figure 52, *C*, was taken on the same patient as Figure 52, *B*, the former preceding the latter by three years. The QRS duration is normal in all leads except CF_2 where it measures 0.13 sec. In addition QRS in CF_2 is splintered, resembling the changes in intraventricular block of the S type. We have referred to this type of intraventricular block as "focal"[5] since it is detected in only one precordial position, and it may be inferred that the intraventricular block is limited to that region of the heart subjacent to the electrode at position C_2. Limb leads alone obviously would not have demonstrated this early phase of intraventricular block.

It is usually difficult or impossible to diagnose anterior wall infarction in the presence of intraventricular block of the common type. Occasionally, however, precordial leads will indicate anterior wall infarction even with concomitant intraventricular block. The electrocardiogram shown in Figure 53, *A*, was obtained on a 63 year old male two days after a clinical episode suggesting myocardial infarction. Intraventricular block of the common type is present but there is no evidence of recent infarction. Figure 53, *B*, taken one week later, demonstrates the changes of recent anterior infarction in the chest leads. The S-T segment in lead CF_4 has become elevated, and in CF_2 it has become more elevated. The T waves are now inverted in these leads, with the characteristic contour of the "coronary" T wave. The S-T segment in lead 3 has become depressed. Figure 53, *C*, was taken five weeks later. The S-T segments in CF_2 and CF_4 are less elevated, and the T waves have become deeper. T_1 is deeper, and T_3 taller. These changes are indicative of the healing stage of an anterior wall infarct. The electrocardiogram in Figure 53, *D*, was taken four years after the

infarct occurred. There is almost complete restitution. Intraventricular block is the principal abnormality seen, without any changes diagnostic of recent or remote infarction.

The diagnosis of anterior wall infarction in the presence of intraventricular block of the S or uncommon type is ordinarily not difficult. The electrocardiogram in Figure 53, *E*, shows a QRS duration of 0.14 sec. with broad S waves in leads 1 and 2. The S-T segment in lead 1 is elevated. In addition T_1 and T_2 are inverted and deep Q waves are

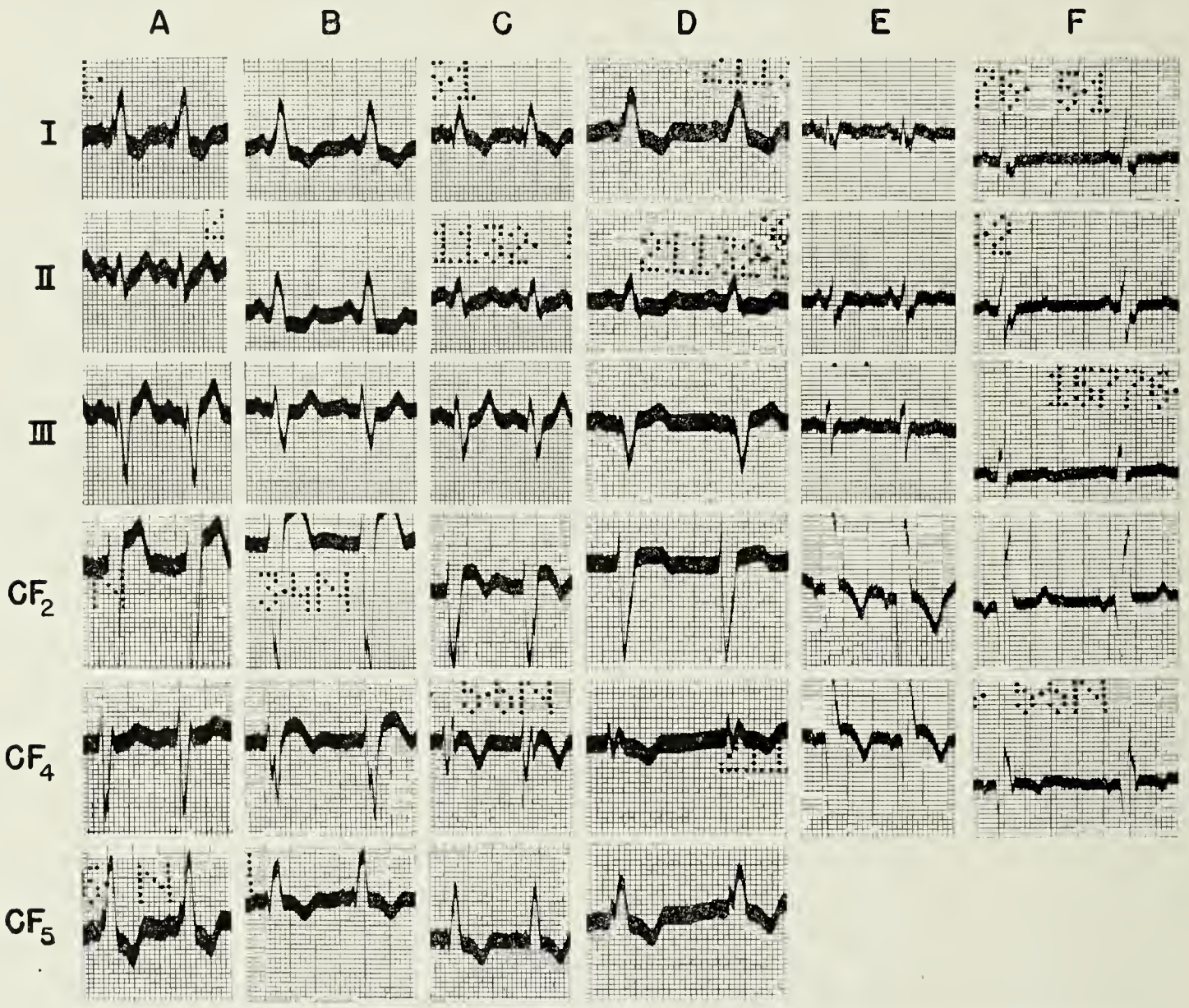

Fig. 53.—Examples of intraventricular block associated with myocardial infarction. (Discussed in text.)

found in CF_2 and CF_4 with elevated S-T segments and deeply inverted T waves. The latter changes point to anterior wall infarction. The changes in the chest leads may persist as the only evidence of remote infarction as shown in the electrocardiogram in Figure 53, *F*, (deep Q waves in CF_2 and CF_4 and inverted T wave in CF_4), taken seven years after the electrocardiogram in Figure 53, *E*.

The diagnosis of anomalous atrioventricular conduction or Wolff-Parkinson-White syndrome is based on the findings of short P-R and prolonged QRS intervals. Characteristically there is slurring of the up-

stroke of the R wave at its junction with the P-Q segment. Occasionally this is more readily demonstrable in chest leads than in limb leads.

The advantages of precordial over limb leads in the diagnosis of intraventricular block are, in general, not as great as in myocardial infarction or heart strain, unless one accepts and utilizes the concept that accurate localization of the block can be determined from precordial leads.

NONSPECIFIC ABNORMALITIES IN CHEST LEADS WITH NORMAL LIMB LEADS

Not infrequently precordial leads will show abnormalities of nonspecific nature when the limb leads are normal. Figure 47, *D*, is such an example. The electrocardiogram was taken on a patient in congestive heart failure. The limb leads are within normal limits, but the chest leads are abnormal because of the small R wave in CF_2 and the small inverted T wave in CF_5 and diphasic T wave in CF_4. Although a definitive electrocardiographic diagnosis cannot be made, the tracing is definitely abnormal. One must be cautious in deriving clinical implications from such electrocardiograms. It is necessary to point out that an abnormal electrocardiogram does not necessarily mean a clinically significant abnormal heart. This is particularly true when the electrocardiographic changes are relatively minor and nonspecific. Clinical studies must determine the significance of these changes. Nevertheless, the precordial leads are very useful in confirming the existence of cardiac disease in the absence of abnormal deviations in standard limb leads.

SUMMARY

It has been the purpose of this presentation to outline the diagnostic advantages of precordial leads over the standard limb leads. Precordial leads are not substitutes for limb leads, but are to be used in conjunction with them. It was repeatedly emphasized that only by employing multiple chest leads does one utilize maximally the specific advantages of chest leads. The practice of taking only one precordial lead is to be condemned because not only will abnormalities go unrecognized, but the physician is liable to a sense of false security if the single chest lead is normal. We recommend the routine use of three chest leads in all cases. We ourselves use CF_2, CF_4 and CF_5.

The advantages of precordial leads may be summarized as follows:

1. Myocardial Infarction
   - A. Precordial leads may show characteristic patterns of myocardial infarction when the limb leads are normal or equivocal. This is particularly true in anterior wall infarction.
   - B. Precordial leads help to localize infarcts more accurately than limb leads alone and may indicate the extent of the infarct.

C. Precordial leads may differentiate cardiac infarction from heart strain.
D. Precordial leads are useful in differentiating cardiac infarction from acute diffuse pericarditis and acute cor pulmonale.
E. Precordial leads may demonstrate anterior wall infarction in the presence of intraventricular block of the common type. In cases of the S or uncommon types of intraventricular block, the precordial leads may show the diagnostic changes of healed infarction long after the limb lead abnormalities have disappeared.

2. Heart Strain
   A. Precordial leads may show characteristic patterns when the limb leads are normal or equivocal. This is particularly true in left heart strain.
   B. Precordial leads facilitate the diagnosis of combined heart strain.
   C. Precordial leads may show left heart strain even when the direction of the electrical axis in the limb leads is normal.
3. Intraventricular Block
   A. Precordial leads may detect early intraventricular block before the limb leads show any prolongation of the QRS interval.
   B. Precordial leads help to localize the block in the right or left bundle branch system in the majority of cases.
   C. Precordial leads may, on occasion, be more diagnostic of the Wolff-Parkinson-White syndrome than limb leads.
4. Precordial leads may detect nonspecific abnormalities when the limb leads are normal.

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RECURRENT ESOPHAGEAL HIATUS HERNIA

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The symptomatology of recurrent esophageal hiatus hernia may present little or nothing which can be said to be characteristic clinically, in the history or in the physical findings. It is possible that in some cases a clue may be afforded when one learns that the symptoms occur in the recumbent position or under conditions which may increase intra-abdominal pressure. Occasionally there may be no symptoms whatever, and the condition may be discovered quite incidentally. When symptoms do occur, they are often the symptoms of some other upper abdominal condition, or the presence of a hernia may produce symptoms of heart or lung involvement. Hiatus hernia is a masquerader, although not the versatile masquerader which some other condition might be, as malaria, for example. The disguise is usually more easily penetrated.

ILLUSTRATIVE CASE HISTORIES

Because of the tendency of hiatus hernia to appear under the guise of some other abdominal or heart condition, or to play a part in the symptomatology of conditions above the diaphragm, it may be worth while to present short abstracts of several case histories illustrating a few of the varied aspects of the symptomatology.

Para-esophageal Hernia

Case I.—This patient, a 64 year old housewife, represents the typical case of hiatus hernia. A few months before coming to the office she had been in bed for over a month with what was diagnosed as "heart trouble." At the time of examination she complained of pain at the left of the xiphoid which she described as being "like a toothache," appearing under certain conditions. The pain radiated to the back at the left of the spine, just above the level of the diaphragm. This pain came on at night about two hours after retiring, and was relieved by getting up, or by assuming a semirecumbent position. The pain also came on when the patient carried heavy articles, such as bags of groceries. The pain was felt, too, upon stooping. The patient was unable to wear a tight girdle because of the discomfort. On some occasions there had been typical anginal pain, radiating to the shoulder and to the left elbow.

The electrocardiogram was normal in every way. On x-ray the heart showed a moderate hypertrophy, with a cardiothoracic ratio of 52 per cent. This enlargement was accounted for by the elevation of both leaves of the diaphgram and was thought to be due to obesity. There was no systolic expansion. Roentgen examination of the gastrointestinal tract showed a large para-esophageal hernia about the

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size of a small grapefruit, with some regurgitation of the barium up into the upper esophagus. The esophagus was tortuous and redundant, and lay posteriorly to the herniated portion of the stomach, above the diaphragm.

The patient was placed upon a diet and, after an initial loss of 15 pounds of weight, with the help of antispasmodic drugs she has remained comfortable, without any attacks, except for a few occasions when the pain has come on while lying down.

Traction Type of Hiatus Hernia

Case II.—This 61 year old housewife was in good health until September, 1945. At this time she began to have severe epigastric pain, coming on in attacks lasting a few and often several hours. There was some pain under the right costal margin on these occasions, but they were of no moment compared with the epigastric pain. This pain did not radiate as a rule, but on two occasions it radiated to a point beneath the left scapula. It appeared most frequently at one or two o'clock in the morning, awakening the patient from a sound sleep. It was relieved in part by alkalies, but not by food, and at times was so severe that opiates were given. On two occasions there was emesis of bright red blood, at one time as much as a cupful. The stools were tarry during and after the episodes. Evidently more blood was lost than was directly accounted for, as the red blood count was 2,700,000 and the hemoglobin 8.6 gm. There was a loss of 15 pounds of weight over a few weeks. Aside from the attacks, the patient complained of weakness and dizziness, due probably to the anemia. An ulcer or early malignancy was suspected because of the bloody emesis.

Physical examination revealed a woman apparently in fair health except for loss of weight and a moderate anemia. There was no tenderness of the abdomen on examination; however, definite tenderness was elicited over the gallbladder when the examination was made in the "drooping position."

Roentgen examination showed a normal stomach and duodenum, but a hiatus hernia was visualized. Gallstones were reported as probable. A second roentgen examinaton, after an acute attack was well over, again showed a normal stomach and duodenum. The roentgenological department did not report a hiatus hernia at this time, but did report a "dilated ampulla." Such a dilated ampulla probably represents a pulling up of the abdominal portion of the esophagus by a shortening of the longitudinal fibers. Visualization showed the gallbladder packed full of small stones.

A cholecystectomy was performed by Dr. S. W. McArthur in May 1946, and there have been no attacks of any kind, or discomfort to date. Physical, roentgen and routine laboratory examinations are normal.

Many years ago, von Bergmann was of the opinion that the epigastric pain in gallbladder attacks was due to a reflex shortening of the esophagus, pulling the stomach up through the hiatal opening. The findings on this patient supported our experimental work on dogs showing a reflex shortening of the esophagus as a result of stimulus from the gallbladder or stomach.

Case III.—This patient is a business executive subject to a great deal of periodic business strain. Until the age of 15 he suffered severe attacks of asthma. These disappeared when his parents removed to an adjacent mountainous region. He had had no gastric symptoms until the last few years, when he began to experience considerable epigastric distress coincident with increased business worries. This was never incapacitating, and the only time lost was due to diagnostic procedures when duodenal ulcer was suspected. No evidence of a gastric or duodenal lesion was ever demonstrated.

His present complaint is pain in the epigastrium, coming on about two hours after meals, not relieved by food or by soda. On going to bed at night he is awakened shortly after going to sleep by a burning pain under the sternum, extending upward to the upper third. Physical examination is negative, except for some slight tenderness in both lower quadrants.

Because duodenal ulcer was again suspected, he was referred to the hospital for a roentgen study. This revealed a perfectly normal stomach and duodenum, but a spastic colon, with diverticula. However, it did show an esophageal hiatus hernia about the size of a lemon.

Routine blood examinations were normal. Fasting blood sugar was normal, as was the blood sugar after a strenuous day's work.

In this case, the only point suggestive of a hiatus hernia was the burning pain under the sternum with the patient in the recumbent position. The symptoms bear a definite relation to strain and overwork, but this would be equally true if a duodenal ulcer were present.

A congenital weakness of the hiatal tissues has been suggested by Akerlund[1] and many others as predisposing to hiatal hernia. In this particular case, the patient's mother had such a hiatus hernia.

Case IV.—A similar causation was suspected in the case of a 57 year old physician who likewise showed symptoms of hiatus hernia when subjected to undue overwork and fatigue. This was so marked at times as to force him to sleep in a semirecumbent position. The symptoms entirely disappeared with a regimen of more rest and relaxation.

In this case a cough developed when the patient was in the recumbent position, or on lifting or bending over. With the lack of optimism which so many physicians exhibit when the symptoms involve themselves, he considered that the cough was due to pulmonary edema, in spite of a very normal heart. The burning sensation under the sternum, associated with the cough in the recumbent position, was given no weight by the patient. Roentgen examination confirmed the diagnosis of hiatus hernia.

Pulsion Type of Herniation of the Stomach

Case V.—A telegraph operator, aged 52, entered the hospital because of dyspnea and attacks of tachycardia on exertion. He stated that he felt very nervous and jittery, but that this was nothing new, that he had always been nervous and apprehensive. He complained also of increased perspiration, which he described as "nervous sweats." Mild exertion brought on a very rapid heart action, with faintness and weakness, and he stated that he had lost consciousness after exertion on a few occasions. The appetite was good, there was no abdominal pain, pyrosis or flatulence, although he had experienced some nausea and vomiting with the "nervous spells." There was no loss of weight.

Physical examination revealed an apparently normal individual. A slight proptosis was recorded, but this was apparently because the history suggested it. The lungs appeared normal, the heart was normal on examination, with a normal mechanism, and a pulse rate of 84. Blood pressure was 148/100. The electrocardiogram was normal, except for an inverted Q_3. The basal metabolic rate was minus 10. A two-meter chest plate showed a normal heart, but there was a shadow lying on the diaphragm, extending to the right of the heart. A barium meal revealed this shadow as the proximal half of the stomach, lying flat on the diaphragm. There was a very redundant esophagus.

The previous history was not significant except for a severe attack of influenza in 1937, followed by a severe cough which lasted for many weeks. The present complaints began at that time.

On medical treatment, the patient returned to work and when last heard from, about six months after leaving the hospital, he had apparently made a satisfactory recovery.

It is safe to assume that the repeated episodes of severe coughing in this case weakened and stretched the hiatal tissues, with the resulting hiatus hernia.

The cough which accompanies hiatus hernia is rather characteristic. It obviously does not come from the nasal pharynx or bronchi, and is a short, dry, irritative cough. It is highly probable that this is another example of the "customer being right," when he tells us that he has a "stomach cough."

Case VI.—An 84 year old woman entered the hospital because of what she termed "fainting attacks." On only slight exertion she became very faint, and was sure that she would faint if she did not immediately lie down. On several occasions she actually lost consciousness, and on the morning of entrance she fainted upon walking across the room. About three months prior to her entrance she began to be troubled by shortness of breath. This became progressively worse until she reached the point where she could not walk at all without dyspnea.

For several years the patient had had pain in the right upper quadrant. There had been acute attacks and, between these attacks, a dull ache. The attacks had been diagnosed on several occasions as cholelithiasis. She had had attacks of emesis coming on suddenly and without effort. The vomited material was bile stained. There was a loss of weight during the year before entrance—just how much, she did not know, but she said that her clothes had "hung loose" on her.

Physical examination revealed a rather obese woman, but one who had obviously lost some weight. There was evidence of a marked anemia. The patient seemed alert and active, within the imposed limits. She was planning a trip by air to visit a son as soon as "we got her well." Physical examination was negative except for tenderness over the gallbladder region and epigastrium. A questionable mass was described in the epigastrium.

The red blood count was 2,550,000 and the hemoglobin 5 gm.; reticulocytes 4. Sedimentation rate was 26 mm. Stools were tarry.

A preliminary diagnosis of carcinoma of the stomach was offered.

A roentgen examination showed the esophagus to be long and not dilated, with a portion of the stomach about the size of a large orange posteriorly and to the left of the midline. There was definite narrowing of the esophageal opening where the stomach passed through the hiatal orifice. The rugae were prominent, and the roentgenologist was of the opinion that he could see evidence of ulceration in the incarcerated portion.

The patient was placed upon medical management and did very well. The blood count returned to a low normal and she was able to take the proposed trip comfortably.

In this case we have another example of the pulsion type of herniation of the stomach through the hiatal opening, due to increased intra-abdominal pressure.

Paravertebral Hernia Through the Hiatal Opening

Case VII.—A 56 year old housewife entered the hospital because of choking and vomiting episodes which she had experienced for the three years before entrance. There was some weakness, shortness of breath and nervousness. She stated that

while eating she would begin to choke on her food and experience a sense of constriction in the neck. At times she felt as though her food remained in her throat and would not go down. Dry foods or cold liquids gave especial difficulty. The appetite remained good, and after emesis the patient felt normal and would resume the meal. These episodes were always more frequent and were worse when eating in public or in the homes of friends. While the symptoms were worse away from home, she still had choking sensations at home, with occasional emesis. After the emesis, there were no symptoms.

The condition had been diagnosed as of nervous origin, and she was told that nothing could be done about it, although because of the "nervousness" several metabolism tests were made. Her weight remained constant.

Physical examination revealed a normal appearing woman except for a moderate obesity. Thoracic organs were normal. The abdomen was protuberant, with firm abdominal walls. No masses were palpable. There was some tenderness in the right upper quadrant, for which no cause was found.

Blood showed red cells 3,640,000, hemoglobin 10.4 gm., and leukocytes 9,750. Roentgen examination was made because of suspected esophageal disease, especially cardiospasm. What it did reveal was an esophagus dilated and displaced to the right, with two diverticula. There was a large paravertebral hernia, extending through the hiatal opening and to the left. This manifested itself by the presence of a large gas bubble in the preliminary chest plate.

The patient was placed upon a reducing, bland diet, and with this, antispasmodic drugs and the avoidance of a tight girdle, she made an excellent recovery. The symptoms ceased for a period of months, only to reappear with her return to her former too abundant diet.

In this case, the patient had a full, protuberant abdomen, with firm abdominal walls. The hernia was obviously of the pulsion type, due to an increased intra-abdominal pressure forcing the stomach up through the hiatal opening.

Esophageal Hiatus Hernia

Case VIII.—The patient, a 50 year old voice instructor, gave a history that showed nothing of importance prior to fifteen years ago. Then began episodes of what were diagnosed as anginal pain, not so much consequent upon effort as during emotional crises, or when success or failure depended upon a very slender thread, or during moments of financial stress, or when, on one occasion, he was inadvertently placed in jail for the night, not because of any wrongdoing on his part. Twice coronary thrombosis was diagnosed, and on one occasion he underwent prolonged treatment with bed rest. On a third occasion, atropine was suggested to the local physician, and there was immediate relief.

Repeated roentgen examination showed an esophageal hiatus hernia at times, and at times no hernia. On one examination a duodenal ulcer was shown, but this was not seen on a subsequent examination.

It is possible here that decreased intrathoracic pressure during singing may have had some bearing upon the incidence of the hernia. The definite relation to emotional crises, however, suggests a shortening of the esophagus during these episodes, and a hernia of the stomach through the hiatal orifice, due to traction from above by the shortened esophagus. When relieved from worry and emotional stress, this patient is completely free from attacks.

Para-esophageal Hernia Associated with Paroxysmal Auricular Fibrillation

Case IX.—A 52 year old railway switchman entered the hospital in May for confirmation of the diagnosis of a compete and total disability. He had been perfectly well until the previous October. At that time, while at work in the railway yard, he stooped to turn over a switch by means of a lever equipped with a heavy iron weight at the end. As he lifted the weight, he became very weak and faint, and returned to the tower with difficulty, stopping to support himself on the cars, which, fortunately, were stationary. He was carried home and the doctor who was called diagnosed a coronary occlusion and advised that he apply for a pension because of complete and permanent disability.

In May he was first examined after he had walked into the office from the train. At that time the heart had a normal mechanism. The next morning when he was examined while in bed in the hospital, the auricles were fibrillating and he appeared uncomfortable. About an hour later, when up and about, he again felt normal, and the heart showed a normal mechanism.

Physical examination revealed a healthy, normal appearing, muscular man, with a rather full abdomen and firm abdominal walls. All laboratory examinations were normal, except for the roentgen examination of the gastrointestinal tract. This revealed a para-esophageal hernia about the size of a lemon.

The patient was placed upon a bland reducing diet, with antispasmodics. He has resumed his former occupation and has remained symptom-free over a period of five years.

We have seen three other cases in which paroxysmal auricular fibrillation was associated with hiatus hernia, and we feel justified in assuming that the herniation produced sufficient stimulation of the vagus to initiate the fibrillation.

These short abstracts from case histories indicate only in part the various guises under which recurrent hiatus hernia may appear. Many more such abstracts would be required to give a really adequate picture, even though they would be simply variations and combinations of the findings set out in these few histories.

Cases of congenital short esophagus or of thoracic stomach have not been cited. They are not at all frequent compared to the incidence of the recurrent acquired type and the clinical significance is of much less importance.

ETIOLOGY

The main etiological features of hiatus hernia are fairly well illustrated in the accompanying case histories. This type of hernia rarely occurs before the fourth decade, usually coming on in later life, as illustrated here. The average age is from 54 to 57. This is easily understood when one considers the importance of senile degenerative changes resulting in loss of elasticity and insufficiency of the hiatal tissues. Schatzke, quoted by Hurst,[2] by using greater than normal intra-abdominal pressure was able to demonstrate herniation in 70 per cent of patients over 60. Abnormal stress, such as would occur in frequent episodes of coughing, could also be assumed to stretch and tear the tissues of the hiatal orifice. The increased intra-abdominal pressure of retching or vomiting would do the same thing.

Increased intra-abdominal pressure from any cause is one of the most frequent factors inducing changes in the adequacy of the hiatal orifice, and in causing the herniation to recur when once the hiatal ring has become insufficient. Obesity, especially when present with firm abdominal walls, is one of the most frequent causes. Large tumors, or ascites, are less frequent causes. Rigler and Eneboe[3] found that 18 per cent of 195 pregnant women showed an esophageal hiatus hernia. Three of ten of these patients, when examined after delivery, still showed such herniation.

The association of hiatus hernia with other upper abdominal conditions, such as cholelithiasis, has been commented upon by many authors, although little has been said in regard to any causal connection. Weintraub and Tuggle,[4] in a review of duodenal diverticula, found hiatus hernia present in 9 per cent of such diverticula, as against 2.4 per cent in 4400 control cases. They did not directly comment upon the possibility that the diverticula might have had some influence in the increased incidence of hernia in such patients. In a personal series of forty-eight cases completely explored roentgenologically, twenty-two showed some concomitant upper abdominal condition, and five, diverticula of the esophagus.

Many years ago von Bergmann[5] suggested that a viscero-visceral reflex, initiated by some source of upper abdominal stimulation, as the gallbladder, might cause a tonic shortening of the esophagus, and pull the cardiac end of the stomach up through the hiatal orifice. He quoted experiments by Kuckuck, in which faradic stimulation of the vagus in the neck of the rabbit shortened the esophagus and even pulled the stomach up above the diaphragm. We repeated the experiment on the rabbit and on the dog[6] with similar results, except that, with the chest closed, we were unable to pull the stomach up through the hiatal ring. Later, with the same electrical stimulation but with the chest open, we were able to show that the traction of shortened esophagus will pull the stomach up above the diaphragm.[7] In addition, we were able to induce a reflex shortening of the esophagus which duplicated the results of electrical stimulation of the vagus, by merely handling the leaves of the liver, or by dilating the gallbladder, or by dilating the cystic duct, or by stretching the walls of the stomach. Clinically, such a reflex is probable in one case in which the hiatus hernia has not recurred since a cholecystectomy, the patient being completely well in every way.

The effect of fatigue and nervousness or emotional factors was mentioned by Hurst.[2] I personally am convinced that purely nervous influences, quite aside from viscero-visceral reflexes, can be the determining factor in a type of hernia caused by traction from above through an esophagus shortened by such influences. Good examples are afforded by Cases III and VIII, also by the physician who had symptoms only when chronically fatigued.

SYMPTOMS

The symptoms are legion, and for the most part, are not specific. In an occasional case there may be no symptoms. Epigastric distress after meals is frequent but, of course, this is seen in many other conditions. In hiatus hernia, the distress or pain, when it occurs, may be projected through to the back, between the scapulae, or to the left of the spine, or under the left scapula. The distress may also be referred to the left of the epigastrium under the left costal margin. There may be a sense of pressure beneath the xiphoid, or a burning sense of fullness extending upward beneath the sternum. This latter may be followed by what the patient refers to as a "burning, acid" eructation, often accompanied by gas. There may be regurgitation of food, or emesis. All these symptoms are suggestive, but not absolutely diagnostic.

Symptoms of a reflex nature occur, such as cardiospasm, or tachycardia, or episodes of paroxysmal auricular fibrillation, or anginoid or actual anginal pain. The anginal pain is a true angina, due to reflex vasoconstriction of the coronary arteries. A reflex vasoconstriction of the coronary arteries, resulting in a marked decrease in coronary flow, was shown by von Bergmann and his associates[5] when the esophagus or the stomach at the hiatal orifice was dilated by means of a balloon. This effect was obviated by vagal section or atropine. We repeated this work with identical results.[8]

Hiatus hernia may not only produce anginal pain, but may simulate a coronary occlusion. Such a case was reported by Reid.[9] Several of our patients with hiatus hernia, giving a history of having been treated for supposed cardiac infarction, showed no electrocardiographic evidence of such an infarction. Nor was there evidence of systolic expansion or postinfarction rigidity on roentgen examination.

DIAGNOSIS

A few points may help to differentiate the symptoms of hiatus hernia from other conditions. The pain may occur soon after retiring, or after about two hours' sleep, appearing sooner than ulcer pain. The symptoms may appear only in the recumbent position, and be relieved by standing erect. Anything which increases intra-abdominal pressure, as bending over, lifting, sneezing or coughing, or retching, may bring on an attack. The patient may not be able to bend over a desk to work, as in drafting. In the case reported by Hurst[2] the patient had to use a high desk, or stand at an old-fashioned bookkeeping desk. Relief may be experienced when intra-abdominal pressure is reduced, as by belching or passing flatus, or following an enema. Aerophagy, or the distention of the stomach by aerated waters, may relieve the symptoms when the distention of the stomach reduces the hernia by pulling it down out of the hiatal orifice.

Secondary anemia may be a symptom and considerable hemorrhage may result either from a small hernia acutely produced, as in Case II, or from a large, incarcerated hernia with ulceration, as in Case VI.

Hiatus hernia should be suspected in every case with a history of anginal pain or paroxysmal auricular fibrillation, especially if there is any reference to posture as a precipitating factor. Every case of angina pectoris should be investigated roentgenologically if the patient's condition permits. This applies also to cases of secondary anemia, where there is no other obvious cause, and regardless of the absence of specific symptoms. Hiatus hernia should be suspected in cases of coronary thrombosis, but of course never to the point of x-ray investigation or interference with the treatment of cardiac infarction until the patient's condition warrants such an investigation.

A great many patients complaining of symptoms of angina pectoris are relieved by treatment for hiatus hernia after the latter is diagnosed.

The diagnostic criteria, such as they are, cannot of course afford much more than a presumptive diagnosis. The history is of great help. Dr. John B. Murphy used to say, "Listen to the patient's story. He is telling you the diagnosis!" Of course, you must be sure that the patient's story does not lead you astray.

Careful roentgen examination by a roentgenologist who is aware that such hernias are frequent, is a necessity always. As has been said above, the hernia may show at one time and not at another. It should always be looked for in the Trendelenburg position as well as in the upright position, and after the administration of barium in that position. The hernia may fill and show when it is filled from below, when it did not show as the barium was swallowed in the erect position, or vice versa. A full, deep inspiration in the recumbent position may demonstrate the hernia, when intrathoracic pressure is decreased, Also, when there is strong presumptive evidence that such a hernia exists, a single x-ray examination is not enough.

There is some question as to the significance of a so-called dilated esophageal ampulla. This probably is essentially a hiatus hernia and represents a pulling up of the abdominal portion of the esophagus by a shortening of the longitudinal fiber.

TREATMENT

In the case of a greatly enlarged hiatal orifice, it is not to be supposed that any medical treatment will give complete relief at all times, under all conditions. In spite of this, medical treatment is usually all that is indicated. In those with a pulsion type of hernia due to increased intra-abdominal pressure, a reduction in weight is the primary indication. In those in whom there is reason to assume that a viscero-visceral reflex results in a shortening of the esophagus, surgical removal of an offending gallbladder will usually give excellent results. The same applies to treatment of a duodenal ulcer.

The patient should be placed upon a bland diet. Small and frequent feedings may be of advantage in some instances. The diet should not produce gas. The patient should eat sitting erect and should not lie down immediately after meals. It should not be necessary to state that he should sit down quietly to his meals, should eat slowly, and should rest before and after meals. Atropine or belladonna, or some drug with an atropine-like action, should be taken regularly before or after meals. Such drugs are best combined with phenobarbital in small doses. There may be an occasional patient who may have to sleep in a semirecumbent position, but this rarely is necessary after a weight loss has been established.

Occasionally interruption of the left phrenic nerve may be of assistance. There will be occasional cases in which surgery is indicated. Harrington has had very good results from surgery in selected cases.

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CLINICAL PROBLEMS OF AGEING AND OF THE AGED

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IT is the purpose of this lecture to acquaint the physician with important clinical problems of the aged; however, the clinical problems of the aged will be best understood when more of the fundamental problems of ageing are known and properly evaluated. There are relatively few studies on the physiology of the aged. It is a most difficult problem to separate the functional changes due to age from those due to disease processes. The physiological and the physical changes in the aged will probably be best understood when more facts on basic physiology and pathology of the aged are available. But it is not only the natural sciences which we must study but also the social sciences, for a knowledge of these sciences will help us solve the problems of the ageing individual in the society in which he lives.

The common complaints of the aged which we wish to discuss are: fatigue, dizziness, high blood pressure, heart trouble and sleeplessness. I list these as the more common complaints. There are many others which are just as common, but it is my belief that those listed above are complaints which are the most important in the patient's opinion and will invariably cause the patient to seek the advice of the physician.

FATIGUE

The aged complain of fatigue or exhaustion on slight effort. "Fatigue" should not be confused with dyspnea associated with cardiac failure. (In such instances evidence of cardiac failure will be evident.) Among the aged complaining of fatigue there are no physical signs other than those we generally find as a result of ageing. The physician is often at a loss to offer any explanation for the fatigue other than the fact that the patient is old in years. Most of the older patients resent this explanation, especially if they have been given this explanation as the cause for other complaints. While emotional tension, anxiety, frustration and the like are offered as an explanation of fatigue, I question whether this explanation is valid for the majority of the older people, and particularly for those who are well adjusted and are secure in their life, and for those who have lost the need for the emotional drive (which is so often considered the cause of fatigue in the younger years). My own impression is that the fatigue of the aged may be associated with a lessened oxygen consumption. It is well known that the basal metabolic rate of the aged is low. It would be of interest to study the oxygen consumption of the aged and determine what factors make

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for a lessened oxygen consumption. Also it would be desirable to study whether the so-called "fatigue products" accumulate in the blood or tissues and are present to a greater degree in the aged than in the young.

Patients seeking relief from fatigue, advise their physicians that they have already tried "vitamins" (though they have shown no evidence of vitamin deficiency), and were "improved" for a time but are "still fatigued." The diet has been "adequate." The aged ask for a "tonic," "liver pills," whiskey, "vitamins." It should be emphasized that all these medicaments may have a valuable psychological effect, and it is advisable to administer such medicaments to the patients. It is best to make a complete physical examination and laboratory study of the urine and blood, and where indicated, x-ray studies, to rule out any organic disease.

The older clinicians often prescribed the elixir ferri quininae et strychinae sulfate, or the elixir gentian glycerinated, and these may still be advised. Amphetamine sulfate, 10 mg., given early in the morning or twice a day has been effective in many instances, but it is wise not to give this drug late in the evening for the patient may be so stimulated that sleep will be disturbed.

Thyroid extract may be of value and is suggested because of the low metabolic rate in the aged. In the past I have not hesitated to use thyroid extract, and my associates and I prescribed as much as 1 gm. (15 grains) daily in our studies on absorption of the gastrointestinal tract in the aged and found no ill effects. Recently, a patient of 72 developed an acute coronary thrombosis, following the use of thyroid extract, 0.065 gm. (1 grain) three times daily for ten days. It is possible that the thyroid extract increased the metabolic rate to such a degree that the demand on the coronary circulation was too great and that a coronary insufficiency was precipitated and followed by coronary thrombosis. Caution is therefore advised in the use of thyroid extract in the aged.

Prostigmine suggests itself as a possible adjunct in the treatment of the fatigue of the aged, but here again caution is advised. It is well to rule out myasthenia gravis in the aged as a cause of fatigue. When the diagnosis of myasthenia gravis is made, the accepted therapy should be employed.

The problem of fatigue in the aged requires further elucidation. It is a most important one, for if we are to advise the aged to continue physical "activities," we must be aware of the amount of fatigue which these activities entail and what burdens they impose on the aged. Certainly, if we recommend employment of the aged in industry, we must know more concerning the fatigability of those unemployed as well as employed. Finally, when we have a clearer understanding of the nature of fatigue in the aged, our therapeutic measures for its relief may become more satisfactory.

DIZZINESS

This symptom is also a common complaint. It may occur alone, or it may be associated with such complaints as headache, nausea, vomiting and constipation. Cathartics or a cleansing enema may relieve this complaint; and because constipation as a cause is so frequent and so obvious it is most often overlooked. However, dizziness or "lightheadedness" as a symptom requires the elimination of the possibility of carotid sinus syndrome, cerebral hemorrhage, cerebral tumor, cardiac failure and functional disturbances as the causative factor. Dizziness is a most distressing symptom to the patient, particularly if it appears on change in posture, such as turning in bed. The patient fears a "stroke." Having heard of a friend or neighbor of similar age, who had the same complaint and who later developed a cerebral hemorrhage, the patient fears that a similar attack is impending and will summon or visit the physician. The physician may find no changes from those noted on previous occasion or, if the patient is examined for the first time, the physician may note no particular findings other than those expected for the age. "Is a stroke impending?," asked the family or the patient. "Is the blood pressure higher?" The physician should answer these questions as best he can, depending on the physical state as revealed by the physical examination. It is most important also for him, however, to evaluate the emotional state of the patient. In the majority of instances reassurance and sedation will solve the problem.

It is wise to rule out a carotid sinus syndrome. The aged have a very sensitive carotid sinus. Pressure on the carotid sinus will produce syncopal attack.

If the dizziness is associated with symptoms of nausea, vomiting or headache, it is important to rule out brain tumor, cerebral hemorrhage, Ménière's syndrome, or functional disease as the causative factor. When these conditions come into question, it is best to hospitalize the patient for complete study.

I wish to relate the story of a patient 72 years of age, who in addition to dizziness complained of headache, vomiting and weight loss. The pulse rate was 46 and the blood pressure was 180. Because of the possibility of brain tumor as a cause of his complaints he was hospitalized for study. In the course of taking his history two important facts were elicited. First, the vomiting appeared only when the patient was agitated. The second important observation was elicited in discussing his sex life. The patient was a vigorous, robust widower, a butcher by trade. Although seventy-two years of age, he said he was "as vigorous sexually as a young man." He had been a widower for a number of years and lived in his own home, which was cared for by an unmarried daughter. "Yes," he had had sexual intercourse since the death of his wife but it was "against his morals," and he wished to marry again, but feared to do so because of his unmarried daughter and the censure of his married children. "Did I think he was foolish?" He was "quite certain that his family would say that he was in his second childhood." Yet, as he said, "he conducted a good business, and all the women who traded in his shop thought well of him." I then asked him if he had any particular woman

in mind whom he wanted to marry. To this he replied "yes." I thereupon advised him that I would discuss the matter with his family. He was reluctant to accept this offer. Nevertheless, I advised his daughters of the true nature of their father's complaint. They were much surprised, but eager to cooperate. The family had a frank and agreeable discussion with their father and urged that he follow my suggestions and be married at once. The following day the patient left the hospital and shortly thereafter was married and became entirely free of all his symptoms much to the relief of his family and his doctor.

This case history illustrates the importance of a careful analysis of the symptoms of which an old person may complain. It also illustrates the need of understanding the social and sexual life of the aged. There is unfortunately a failure on the part of many to appreciate the fact that the aged are normal people with normal desires. The normal aged are often frustrated not only by their own inhibitions but by the restrictions which social customs have imposed upon them. When finances or the economic aspects enter into similar situations the problem of adjustment becomes much more complex and it is then that the family may not be as agreeable as in the case illustrated.

The social adjustment of the aged is indeed a complex problem and the physician must be aware of the social situations which precipitate functional syndromes. The social adjustments of the aged have been made more difficult by the changes which have taken place in family life. The family has not only become smaller in size, but youth has felt the need "to live their lives" apart from the aged. In many instances this is best for the young as well as the old, but there is probably no fixed rule for the best procedure to follow and the social adjustment had best be made on the merits of the individual case.

HIGH BLOOD PRESSURE

The aged as well as the younger patients wish to know "how high is the blood pressure." This desire is a symptom not of age but of anxiety. The lay public as well as some of the medical public accept the idea that the normal blood pressure is 100 plus age. Therefore if a person of 70 years is advised that his pressure is 190 systolic, he is of the opinion that he is sick and may have a stroke at any time. Most patients are disturbed by the knowledge that their blood pressure is high.

The complaints of patients who have anxiety concerning high blood pressure are headaches, dizziness, rapid pulse, irregularity of the heart beat, precordial distress, anginal syndrome, constipation and fatigue. These are the symptoms also of the ageing process. These are also the symptoms of hypertension. The patient must be thoroughly examined and studied before the physician makes a diagnosis. All three, anxiety, high blood pressure and old age, may be present in the same patient and yet the patient may be a normal old person. What is the dominant picture at the moment? This must be determined by the

physician. In the absence of cardiac and renal insufficiency and negative electrocardiographic findings, the patient may be reassured. In many instances some degree of renal impairment or cardiac insufficiency may be evident. The physician should exercise caution in a statement of diagnosis and prognosis. As far as possible it is wisest for the physician not to discuss the height of the blood pressure with the patient but in some instances it cannot be avoided. The family of the patient should be given an adequate explanation of the nature of the hypertension and the degree of cardiac and renal involvement. When anxiety dominates the picture reassurance is the best remedy. When a maladjustment or social situation exists, an attempt should be made by the physician to adjust the situation. In some instances, a social worker or the psychiatrist may be helpful.

As for active treatment of hypertension in the aged, I have made use of no specific drugs to reduce the blood pressure. It has been my experience that sedations such as the elixir triple bromides or elixir phenobarbital are as effective as any other drugs. If hypertension is associated with evidence of cardiac failure, moderate dosage of digitalis is advisable and with improvement in cardiac status the blood pressure will fall. For cerebral encephalopathy associated with hypertension, venesection or the intravenous administration of hypertonic (50 per cent) glucose may be of value. In the absence of any evidence of complications it is best to guide the patient by simple measures such as moderate activity, moderate dietary habits and general reassurance.

A blood pressure of 120 systolic or lower may be present in the aged for many years. Arteriosclerosis is frequently associated. In such instances, cerebral thrombosis or coronary occlusion are not infrequent. I have observed some patients at 70 years of age whose blood pressure has been 120 systolic for many years who suddenly develop hypertension with systolic readings of 180 to 240. I have observed this particularly in some of the bedridden patients who developed an acute pyelonephritis. I believe that this condition is often overlooked and invariably I have observed that these patients developed such complications as cerebral hemorrhage, uremia or cardiac failure.

CORONARY THROMBOSIS

Coronary thrombosis may manifest itself in the aged, with the typical symptoms of severe pain in the chest and the signs of circulatory collapse. Such instances are readily recognized. However, there are many instances in which coronary thrombosis occurs with a minimal amount of symptoms—the well-known "silent coronary"—no pain, but circulatory failure, which may come on suddenly or appear gradually. If an anginal syndrome has previously been known to exist, the recognition of the nature of the cardiac failure is more

readily established. The electrocardiographic changes may reveal evidence of coronary insufficiency or again the electrocardiogram may be equivocal.

As in the middle aged, the coronary disease of the aged may appear as a *gastrointestinal syndrome* and be regarded as *indigestion, gastritis* or *gallbladder disease* by the physician as well as the patient. In a previous lecture I have emphasized the need of differentiation of these conditions from coronary disease. I have also pointed out the association of these conditions in the same patient. It is a routine procedure in my practice to make a complete gastrointestinal study—particularly x-ray studies—of a patient with coronary disease. In a like manner, a complete study of the heart is made in any person with suspected peptic ulcer or gallbladder disease. I have also pointed out that the epigastralgia or anginal syndrome in the aged and middle aged may be due to "functional" gastrointestinal disease or "functional" cardiac problems.

In the aged, *the syndrome of abdominal pain, "angina abdominalis"* may be due entirely to referred pain from coronary thrombosis or occlusion. It is most important for the clinician to differentiate "angina abdominalis" due to coronary disease from abdominal pain due to many other causes, such as acute pancreatitis, perforated peptic ulcer, gallstone colic and many causes of intestinal obstruction not the least of which is arteriosclerosis of the mesenteric arteries.

INSOMNIA (SLEEPLESSNESS)

The aged complain of sleeplessness. However, the aged also complain that they fall asleep during the day at frequent intervals. This is a common observation. The complaint of the aged is that they do not sleep at night and it is because of this that most old people seek relief. An old patient said, "I go to bed so early in the evening and sleep, but I am awake at midnight and cannot sleep the rest of the night. I am so fatigued the next morning that I am unable to do anything all day and therefore sleep on and off during the day. If I take a 'sleeping pill' during the night, I am depressed or 'woozy' the next day." The statement of this patient is typical.

The sleep requirements of the aged according to Best and Taylor are five to seven hours daily. It is difficult to estimate the actual number of hours which most old patients actually sleep. Most of the older patients state that they do not get five to seven hours of sleep. My experience has been that among old patients who are occupied at work and are well adjusted, insomnia is not a frequent complaint. I am also of the opinion that the average aged person gets at least the required five hours of sleep. The complaint is, however, more common among the aged patients who are unemployed or who live alone and have nothing to do all day long. It is not uncommon among

women who spend their day and night in the excitement and overstimulation of bridge and keno. I believe insomnia is prevalent among the aged who are overstimulated from any cause, whether it be maladjustment, insecurity or anxiety. I am advised that the aged in most Homes for the Aged are not troubled by insomnia because of the security and routinization of life.

ASTHMA

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Asthma is the term used to describe a symptom complex characterized by attacks of dyspnea followed by wheezing and coughing, whose etiology is hypersensitivity. The term "bronchial asthma" is a misnomer because asthma by definition is bronchial in origin.

The Greek physician, Aretaeus, in the second century, A.D., gave a vivid picture of the asthmatic attack which is so descriptive that it bears repeating. The symptoms of its approach are heaviness of the chest; sluggishness to one's accustomed work, and to every other exertion; difficulty of breathing in running or on a steep road; one is hoarse and troubled with cough, flatulence and extraordinary evacuations in the hypochondriac region; restlessness; heat at night—small and imperceptible; nose sharp and ready for respiration. "But if the evil gradually gets worse, the cheeks are ruddy, eyes protuberant, as if from strangulation; a rale during the waking state, but the evil much worse in sleep; voice liquid and without resonance; a desire of much and of cold air; they eagerly go into the open air, since no house sufficeth for their respiration; they breathe standing as if desiring to draw in all the air which they possibly can inhale; and, in their want of air, they also open the mouth as if thus to enjoy the more of it; pale on the countenance, except the cheeks, which are ruddy; sweat about the forehead and clavicles; cough incessant and laborious; expectoration small, thin, cold, resembling efflorescence of foam; neck swells with the inflation of the breath; the precordia retracted; pulse small, dense, compressed; legs slender, and if these symptoms increase, they sometimes produce suffocation, after the form of epilepsy.

"But if it takes a favorable turn, cough more protracted and rarer; a more copious expectoration of more fluid matters; discharges from the bowels plentiful and watery; secretion of urine copious, although unattended with sediment; voice louder; sleep sufficient; relaxation of the precordia; sometimes a pain comes into the back during the remission; panting rare, soft, hoarse. Thus they escape a fatal termination. But, during the remissions, although they may walk about erect, they bear the traces of the affection."

PHYSIOLOGY OF ASTHMA

Asthma is produced by a constriction of the bronchioles throughout the entire lung parenchyma either by a spasm of the fine circular

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smooth muscle of the bronchiole or by an edema of the mucous lining of the bronchiole or a combination of both factors. The antigen usually gains access to the lung by way of the blood stream.

The bronchiolar musculature is under the control of the autonomic nervous system of which the sympathetic or thoracolumbar division serves as the dilator supply and is indeed the dominating influence normally over the constrictor parasympathetic or craniosacral division of the autonomic system. In man, one of the responses of the body to an antigen is the constriction of the bronchiolar musculature of the lung, leading to diminished air supply to the alveoli and to a relatively inelastic, indistensible lung. This situation, of course, results in a marked lowering of the vital capacity to the "dyspenic point" and the patient is in much the same distress as a cardiac. Indeed, the mechanism by which the dyspnea is produced is comparable, in that it is the vagal reflexes inaugurated by this inelastic lung which affect the respiratory center so as to produce tachypnea and dyspnea. Experimentally, as Harrison has shown, sectioning of the vagi in an inelastic lung markedly decreases or abolishes the dyspnea. In order to reverse the sequence of events just described, we resort to the use of a powerful sympathomimetic drug, epinephrine, whose action in stimulating the sympathetics result in a dilatation of the bronchioles and a vasoconstriction of the blood supply to the bronchial mucosa, these actions accomplishing a free access of air and a diminished secretion of mucous plugs. By so returning the lung to its normal elasticity, the vital capacity returns to normal and the dyspnea is abolished.

PATHOLOGY

Many workers in pathology performing autopsies on patients dying in acute attacks of asthma have regularly found a narrowing of the lumen of the smaller bronchi and bronchioles due to the following causes:

1. A hypertrophy of the fine circular muscles and an increase in the thickness of their walls. The many mucous glands which lubricate the bronchi also become enlarged and secrete much more mucus than normally.

2. An edema of the mucous membrane lining the bronchi. The microscopic anatomy reveals eosinophilic infiltration and an increase in mononuclear cells. Charcot-Leyden crystals and Churchmann's spirals are usually found in the mucosa and in expectorated sputum. Various degrees of emphysema and bronchiectasis may be seen in chronic cases.

DIAGNOSIS

The diagnosis of asthma is made from the clinical symptoms which characterize the disorder together with the physical findings and the demonstration of the criteria of allergy, such as positive skin tests, and other confirmatory laboratory evidence.

Symptoms.—The asthmatic attack usually comes at night, often with an insidious onset. The first sensation the patient notices is a difficulty in breathing, his chest is "heavy," and he finds that he cannot remain in the recumbent position but must sit up or stand up in order to breathe. Then the patient will begin to use the accessory muscles of respiration and by this time will describe wheezing noises coming from his chest during respiration. He will also cough desperately, with or without expectoration. These symptoms may last from a few minutes to many hours or days, if untreated. Expectoration of mucous plugs with tenacious sputum herald the close of the attack. Asthmatic patients may complain of continuous coughing without dyspnea or wheezing; this is particularly true in children. Characteristically, the patient has no symptoms between attacks. Physical exertion, overeating, or the onset of a cold may precipitate an attack of asthma; however, very often an attack may come on with apparently no cause.

The natural course of untreated asthma is increasing frequency and severity of attacks which may ultimately result in persistent asthma or status asthmaticus. In status asthmaticus, the patient wheezes constantly and the cough and shortness of the breath are present continuously; any manner of activity is difficult and the only way these patients can get any air into their lungs is to assume a semisitting position, bent forward, attempting to expel that air which they have succeeded in inspiring. Although the patient has marked difficulty in both the inspiratory and expiratory phases of respiration, the expiratory phase is attended with the most distress. The symptoms may resemble those of a state of shock with cold, clammy perspiration, subnormal temperature and a rapid thready pulse; indeed, the patient is suffering from allergic shock.

In children, quite commonly, an attack of asthma is ushered in with a high temperature and very often pneumonia is suspected or wrongly diagnosed.

Physical Findings.—On inspection, the patient is observed to be breathing with difficulty, using the accessory muscles of respiration with a corresponding widening and fixing of the intercostal spaces, with the ribs in a horizontal position as seen in deep inspiration. On percussion, a hyperresonance throughout, more marked over the bases of the lungs, can be elicited. On auscultation, numerous wheezing, sibilant and sonorous rales are heard throughout the chest with the expiratory phase definitely prolonged over the inspiratory phase. It should be borne in mind that an asthmatic person may be in acute distress without prominent wheezing or rales and that one may often detect fine rales by placing the diaphragm of the stethoscope at the patient's open mouth and having him breathe at it.

Laboratory Findings.—The blood and sputum characteristically show an increase in eosinophils which may range from 5 to 50 per

cent of the differential count, and this is one of the most common findings in asthma. Early in the attack there may be very little sputum, but at its termination expectoration of mucous plugs containing Charcot-Leyden crystals and eosinophils usually occurs. The urine shows no abnormal findings in uncomplicated cases; the blood chemistry reveals normal values including the calcium content in which I have never seen a discrepancy.

Electrocardiography usually shows no variations from the normal between the attacks; however, during an asthmatic attack there are variations from the normal which are difficult to interpret but which usually revert to normal when the attack is over. In the acute attack, electrocardiography may reveal changes characteristic of acute coronary insufficiency. For accurate evaluation, it is therefore advisable to take electrocardiograms after, rather than during, an acute attack.

Roentgenography and *fluoroscopy* of the chest do not reveal any abnormal findings in the uncomplicated asthmatic; however, chest plates of chronic asthmatics may show evidence of heavy hilar shadows, bronchiectasis, emphysema, or a combination of these. The fluoroscopic findings during an asthmatic attack are an emphysema with depressed diaphragmatic arches. The heart is of normal or diminished size.

DIFFERENTIAL DIAGNOSIS

In adults, asthma must be differentiated from such conditions as paroxysmal nocturnal dyspnea of cardiac disease, mediastinal tumor, pulmonary tuberculosis, pressure in the chest from aneurysm or foreign body, bronchogenic carcinoma of the lung, chronic bronchitis, chronic emphysema, cor pulmonale, chronic glomerulonephritis and substernal thyroid.

Paroxysmal Nocturnal Dyspnea or Cardiac Asthma.—Cardiac asthma may be confused with asthma when occurring in individuals who are in the age group in which degenerative heart disease is common. The differential diagnosis is important because the difference in treatment is so pronounced. Dyspnea due to cardiac disease in most cases is due to left ventricular failure and is caused by marked passive congestion of the lungs. Attacks usually occur at night after the patient has been asleep for some time. He then is suddenly awakened by a feeling of choking, gasping and intense inspiratory dyspnea. These attacks may be brought on by reflex stimulation of the respiratory center such as coughing, a desire to urinate, or sudden awakening following a disturbing dream. Sitting upright in bed lessens the dyspnea by increasing the pulmonary ventilation. On examination, the patient may be found to have hypertension, with enlargement of the heart and other evidences of chronic heart disease such as coronary artery disease or luetic aortic disease. The physical findings may reveal wheezing, sibilant and sonorous rales similar to those found in asthma. It

must be remembered that the middle-aged patient may have both asthma and some degree of heart disease and the latter may precipitate dyspnea by the following mechanism: The pulmonary congestion incident to left ventricular failure will produce bronchoconstriction and wheezing by acting as a nonspecific irritant to which the lung responds as it once did to an antigen. This sequence thus constitutes a conditioned reflex. Of great help in evaluating the differential diagnosis is the history of a preceding or associated hay fever or rhinitis, a sensitivity to some food, a family history of some allergy, a history of manifestation of allergy in childhood, recurring colds or bronchitis, urticaria, migraine, eczema or cyclic vomiting.

Asthma usually occurs in younger individuals. In asthma, the blood pressure is usually low, and the venous pressure is normal or subnormal; indeed, this constitutes a valuable aid in the differential diagnosis because cardiacs so commonly have increased venous pressure. The presence of positive skin tests plus blood eosinophilia tilts the balance toward a diagnosis of asthma.

Mediastinal Tumor.—Mediastinal tumor produces dyspnea by pressure or displacement of the trachea. The findings are increased dullness over the upper portion of the sternum plus fluoroscopic and roentgen visualization of an increased density over this same upper portion.

Pulmonary Tuberculosis.—Patients suffering from pulmonary tuberculosis may also have asthma, on an allergic basis, due either to the ordinary sensitivities or to the development of a sensitivity to the products of the tubercle bacillus. Careful physical examination may reveal fine, moist rales over one or both apices and infraclavicular areas. Fluoroscopy and x-ray usually demonstrate destruction of lung tissue in the apices or infraclavicular areas. The presence of afternoon fever, persistent rapid pulse and other characteristic toxic symptoms help in the diagnosis, and the finding of tubercle bacilli in the sputum clinches the diagnosis.

Aortic Aneurysm.—The findings of widened aorta, with expansile pulsation and the presence of a bruit over the second intercostal space to the right or left of the sternum in an individual with positive serology, plus fluoroscopic findings of a pulsating mass synchronous with the pulsation of the aorta, spells aneurysm.

Foreign Body.—A foreign body in a bronchus, occuring especially in children, may present unusual difficulty in diagnosis. The important findings are unilateral wheezing and congestion of one side of the chest. Bronchoscopic and x-ray visualization will usually localize the foreign body.

Primary Bronchogenic Carcinoma of the Lung.—The first manifestation of a primary bronchogenic carcinoma of the lung may be wheezing and cough occurring in a patient of middle age. Usually, there will be an accompanying expectoration of blood-tinged sputum and

physical findings of impaired resonance to dullness over an upper lobe with suppressed breath sounds. These findings are compatible with those of atelectasis. Fluoroscopic and x-ray examination demonstrate an infiltration in an area of a lung surrounding a bronchus. Lipiodol instillation in the bronchial tree plus bronchoscopy will usually show the carcinomatous infiltration.

Metastatic Carcinoma of the Lung.—The diagnosis here is made on the history of the x-ray findings of cannon-ball distribution of infiltration throughout both lungs.

Chronic Bronchitis.—A history of repeated upper respiratory infections with cough and expectation of purulent material plus findings of coarse, moist rales along the larger bronchi is suggestive of chronic bronchitis.

Chronic Emphysema with or without Cor Pulmonale.—A history of occupation is important, such as strenuous athletics, lifting, and other physical exertion such as is performed by musicians playing wind instruments. Chronic asthma itself may lead to an emphysema. If the emphysema is severe enough, a cor pulmonale with right heart failure may be expected and may be diagnosed by the presence of cyanosis, increased venous pressure, and enlargement of the right heart, in addition to the sibilant and sonorous rales heard on auscultation as well as the barrel chest seen on inspection. X-ray confirms the diagnosis.

Chronic Glomerulonephritis.—This condition may simulate asthma in two ways; first, by the production of a hypertensive heart disease with cardiac dyspnea, and secondly, by the hyperpnea present in the acidosis of the pre-uremic or uremic state. This diagnosis can usually be made without difficulty on the basis of the blood pressure, urine findings and blood chemistry.

Substernal Thyroid.—A substernal thyroid enlargement often gives rise to the sensations of choking and gasping and wheezing. This condition can be diagnosed by fluoroscopic and x-ray findings of widening at the upper end of the mediastinum, constituting a type of mediastinal tumor. Basal metabolic rate determinations and blood chemistry may aid in the diagnosis if the thyroid is hyperactive.

Enlarged Tracheobronchial Lymph Nodes and Enlarged Thymus in Children.—These conditions should be remembered in considering dyspnea in children and can be ruled out by fluoroscopic and x-ray examination.

THE ETIOLOGIC DIAGNOSIS AND TREATMENT OF ASTHMA

There are three major categories of asthmatic patients: One group consists of patients with the frankly allergic type of asthma, in whom positive skin tests and eosinophilia in the sputum and blood can be demonstrated. The second group consists of patients usually but not always past 50, who give negative skin tests and no family history of

allergy and in whom the asthma is preceded by frequent attacks of upper respiratory infections, perennial rhinitis or an attack of pneumonia. The third group comprises those patients in whom there is an element of the previous types, with various degrees of dominance of one or the other. The frankly allergic group of asthmatic patients comprise the large majority, making up as much as 75 per cent of the total.

Group I. The Frankly Allergic Group.—Close attention to the history will usually elicit some allergic disturbance in the patient, perhaps years ago, such as a seasonal rhinitis, which recurred for years but which was so slight that no significance was attached to it, the patient believing that these were merely attacks of acute coryza. Also, attacks of perennial rhinitis would occur for years under the guise of "colds." Sometimes urticaria or a food intolerance disturbed the patient years ago but only a carefully taken history will uncover these significant findings and permit their correct interpretation in the light of the present asthmatic symptoms.

The etiologic agent in most instances can be found in the inhalant groups, such as chicken, goose, duck or bird feathers, dog or cat hair, orris root, pyrethrum, horse dander, cottonseed, linseed, silk, wool, rabbit hair, house dust, glue, goat hair, kapok, mattress dust, molds and yeasts in the air and house and various pollens. Foods by inhalation as may occur in bakers, millers and housewives are also common causes, and ingested foods may play a role. Farmers exposed to corn, rye, barley or other grain dusts and smuts may be affected with a severe type of asthma, following their inhalation. As an example of the frankly allergic type developing in an individual past 50, I quote the following case from my practice: A druggist at the age of 50 became sensitized to the spores of lycopodium dust, which is used in drying pills and capsules. Skin tests to powdered lycopodium were positive and the complete elimination of lycopodium from his environment resulted in a complete disappearance of symptoms.

In testing these patients, it is important to make not only cutaneous or scratch tests but also intradermal and even passive transfer tests in order to determine the causative factor. All of these tests, including passive transfer, must be negative before one classifies the patient in Group II.

In my own practice, I have practically abandoned the scratch test because it is so much less sensitive than the intradermal test. This is particularly important in testing with foods since the dried food extracts that are used in scratch testing are not nearly so active and potent as the fresh liquid food extracts prepared for intradermal testing. One must be extremely cautious in testing intradermally with cottonseed, linseed, kapok and fish extracts in very sensitive individuals since alarming and even fatal systemic reactions have occurred and been reported in the literature. Often a clue to these sensitivities may

be uncovered in a carefully taken history. These patients may come down with asthma following exposure to food or cooking odors especially that of fish, or following the ingestion of cottonseed oils or dressings containing these oils. When such a history is obtained, particularly in children, it may be safer to employ the scratch test first and then, if this is found negative, the intradermal test, using a very dilute extract.

Environmental control of these patients is essential to relieve their asthma. Impervious pillow and mattress covers, as well as complete house dust precautions should be insisted upon. Other inhalant factors etiologically present, as determined by skin tests, must be avoided entirely. This admonition is simple enough, yet in practice it is very difficult to enforce unless patients are carefully informed on how to avoid inhalant substances in the various forms to which they are exposed unknowingly. Visits to the home by the physician are often necessary to point out errors in omission when patients actually thought they were eliminating certain inhalant factors. To illustrate, a patient who reacted strongly to rabbit hair and horse hair obtained relief only after the complete elimination of an animal hair padding under the carpeting, which she had completely overlooked. It was very difficult to convince this patient, in spite of the fact that upon a short stay in the hospital on several occasions the symptoms would clear up in a few days only to recur when the patient returned home. It is also important to hyposensitize these patients, especially those sensitive to house dust, orris root, silk, molds, yeast and pollen. It is virtually impossible to escape these inhalant substances either in the home or outdoors.

Group II. No History of Allergy Obtainable; Negative Skin Tests.—In this group of patients, changes in environment, diet or weather have no influence on their asthma. The asthma is usually severe and may even be rapidly fatal. Pathologically, there seems to be more secretion in the bronchi and less spasm than in the frankly allergic group. There may also be infection in the paranasal sinuses and bronchi, and complications of bronchiectasis and emphysema seem to follow early. There are many theories at the present time as to the etiology of asthma in these patients; perhaps the most plausible one is the hypothesis that an allergy is developed to products of infection. The first step in the treatment of these patients is to make sure that they belong in Group II, that skin tests and passive transfer tests are negative. Then, the control of the sinusitis and nasal infections by proper local and systemic means is in order. Control of upper respiratory infections in general is essential. Sometimes the procedure of bronchoscopy, which eliminates the excess secretions and pus, may give some relief. Potassium iodide, 0.6 to 1 gm. (10 to 15 grains) three times a day, often helps to liquefy secretions and aids in expectoration as does ammonium chloride, 1 gm. (15 grains) four

times a day. The following prescription has been found very useful in this type of asthma:

℞: Spirits chloroform ..... 0.35 cc. (ɱv)
Apomorphine hydrochloride ..... 0.065 gm.(gr. i)
Potassium iodide,
Tr. lobelia .....āa 15.00 gm. (cc.) (ʒiv)
Syrup of wild cherry .....qs. ad. 120.00 cc. (ʒiv)
Sig.: 4 cc. (1 dram) well diluted with water every four hours.

Aminophylline, 0.5 gm. (7½ grains) in 10 or 20 cc. of normal saline, given intravenously, often is beneficial in this group. Aminophylline in rectal suppositories, 0.33 to 0.5 gm. (5 to 7½ grains) at bedtime is often helpful.

Epinephrine 1:500 in oil, preferably sesame oil, 1 cc. intramuscularly, may control the wheezing for as long as twenty-four to forty-eight hours, but may be repeated every four to six hours if needed. (Note: The ampule should be immersed in warm water and shaken vigorously before opening and using so as to get the particles of epinephrine in smooth suspension.)

For the distressing cough, hycodan bitartrate (Endo Products) in 5 mg. tablets may give considerable relief if given every four to six hours. This product is a derivation of codeine, yet has none of the undesirable properties of codeine and is not habit-forming. I have never noted allergic symptoms from this drug as contrasted to the frequent occurrence of urticaria and dermatitis following codeine. The use of morphine, pantopon and demerol hydrochloride are to be condemned in asthma since they are habit-forming and so depress the cough reflex center that the patient is not able to bring up the tenacious mucus plugs and sputum necessary for relief and may virtually drown in his own secretions.

In status asthmaticus, often the judicious use of epinephrine, aqueous and in oil, and of ether and oil per rectum and sedation have failed. Helium and oxygen, as originally advised by Barach, are used in severe paroxysms of asthma and administered through the Boothby-Lovelace-Bulbulian (B.L.B.) mask, which fits over the nose, leaving the mouth open enough for eating, talking and drinking. The gas mixture consists of 20 per cent oxygen and 80 per cent helium and its beneficial effects depend on its low specific gravity as compared with that of oxygen. Tanks of helium-oxygen and of pure oxygen are connected to the mask by Y valves and, as the patient improves, more oxygen and less helium are used. Great caution should be exercised in using drugs in asthma since many patients are sensitive to drug compounds such as aspirin, phenobarbital, pentobarbital, codeine and morphine. Unfortunately, these complex chemicals do not give reactions by skin tests and the only way to determine sensitivity to them is to use them, but the trial has not always been safe or easy. It is far safer to use those drugs having simpler chemical formulas, such

as bromides, chloral hydrate and paraldehyde. Five per cent glucose in 1000 cc. of normal salt solution intravenously may be extremely helpful in patients who are dehydrated, and as much as 2000 cc. can be safely given in a twenty-four hour period. Ether and olive oil, a mixture of equal parts, 150 cc. to 200 cc. given per rectum every six to eight hours, if needed, often aids materially in shortening the course of a severe asthmatic attack. The results of vaccine therapy remain a controversial issue. Some workers claim good results with autogenous vaccines and others claim equally good results with stock vaccines. My own opinion of vaccines in this type of asthma is that they exert a nonspecific effect similar to that obtained with any foreign protein injection such as proteolac, milk protein or typhoid vaccine. If the vaccine produces a local reaction at the site of injection, improvement of the symptoms may occur temporarily, only to recur again. The use of vaccines in general has been very disappointing.

Group III. Mixed Group.—The third group of asthma patients comprises those who originally were frankly allergic patients and then perhaps years later the allergy became complicated by infections in the bronchial tree and paranasal sinuses. It is important to test these patients thoroughly and make an attempt to eliminate inhalant as well as food allergens which originally caused the asthmatic symptoms. The treatment of the sinuses and bacterial infection in the bronchi resolves itself into conservative local measures to aid drainage and general measures aimed at increasing the general body resistance. The use of iron, arsenic in small doses as Fowler's solution, 0.2 to 0.35 cc. (3 to 5 minims), and vitamins may be beneficial if indicated. Radical nasal surgery has done more harm than good, whereas conservative local measures plus adequate control of the allergic background offers the greatest hope for relief in these patients.

ILLUSTRATIVE CASES

Case I.—Mrs. L. P., aged 24, was seen because of asthma, which began two years ago during her sixth month of pregnancy and has persisted since. There was a past history of sneezing and rhinorrhea throughout the year for several years and a history of chronic asthma in her father. Examination disclosed sibilant and sonorous rales over both lungs and nasal examination revealed hypertrophied, boggy inferior turbinates. Eosinophils in the blood were 9 per cent, with a normal total leukocyte count. Intradermal skin tests were strongly positive to feathers, dust, mattress dust, wool and animal hair. Smaller reactions were obtained to chocolate and milk. Instructions were given to cover the pillows and mattresses with nonallergic covers and chocolate and milk were excluded from the diet. Hyposensitization was given to an autogenous house dust and mattress dust extract. The patient rapidly improved and has not experienced an asthmatic attack or rhinitis for the past three years.

The interesting feature of this case is that the patient had been allergic for years before her pregnancy. During the last three months of her pregnancy she literally forced herself to drink more milk than

she had been accustomed to, in spite of a dislike for milk. This procedure, plus the added strain of pregnancy, upset the allergic balance and the summation effect of the exposure to several antigens combined to produce a severe asthma, which persists until their removal.

It is of the utmost importance that allergic pregnant women should not partake of unusual amounts of any particular food, especially where there is a dislike for it, since they may be potentially sensitive to the food but may show only slight or no symptoms on small quantities. Vaughan has termed this the "balanced allergic state," and a summation of several antigens, plus the added strain during the latter part of pregnancy, may upset this balance with the production of symptoms.

Case II.—J. L., a boy aged 10, came in because of hay fever from August 15 to September 15, and asthma throughout the year. The hay fever symptoms were present for four years and the asthma began two years ago. There had also been periodic attacks of urticaria during the past four years. In the family history, the father has a perennial rhinitis and a contact dermatitis on the hands, caused by handling parsnips. The paternal uncle has hay fever. Examination disclosed wheezing, sibilant and sonorous rales over both lungs. Previous pollen injections for hay fever and one year of treatment with an oral pollen preparation gave no relief. On complete intradermal testing, it was found that large reactions were obtained to giant and short ragweed, corn, cantaloupe and shrimp and smaller reactions to cottonwood tree pollen, cat hair, cholocate and tomato. Chocolate, tomato, corn and cantaloupe were removed from the diet. A cat was ordered removed from the home and treatment was given to the ragweeds and cottonwood pollens. Under this regimen, improvement was rapid and the hay fever was well under control.

Case III.—Mr. A. L., aged 32, had asthma for three years. He also had a dog in the house for the same length of time. Tests revealed a large reaction only to dog dander. An attempt was made to hyposensitize him to dog dander since he was not willing to dispose of the dog. Asthma persisted, however, and he was not relieved until the dog was disposed of and the house thoroughly cleaned of dog hair. The asthma was relieved completely when this was done.

These cases emphasize that complete contact with the offending allergen must be insisted upon before relief can be expected.

Case IV.—Mrs. G. F., aged 25, wife of a physician, complained of rhinitis occurring throughout the year, for three or four years, accompanied by sneezing, itching of the nose and a clear, watery nasal discharge. She had been treated by several otolaryngologists, and on two occasions the antra were punctured. About three weeks after the last antral puncture, cough and asthma developed and wheezing would occur three to four times during the week. In the history, one uncle had hay fever. There was an additional history of a chronic colitis in the patient for many years, and an internist suspected a gastric ulcer, although x-ray examination of the gastrointestinal tract was negative for ulcer.

Examination revealed a pale undernourished woman, with considerable cough and wheezing bilaterally over both lungs. The blood eosinophilia was 16 per cent. Intradermal tests were strongly positive to all feathers and egg white, beets and banana. This patient was employed as a social worker in a sanatorium where

she was in contact with chickens and ducks kept in the yard. Elimination of contact with feathers, and avoidance of eggs, beets and banana in the diet, stopped the asthma. She gained weight rapidly and the gastric and colonic symptoms promptly cleared. The patient's husband informed me some three years later that he was the proud father of a baby son, and that no further symptoms of rhinitis, asthma or colitis had appeared.

This case illustrates an allergic response to inhalants and foods, beginning with rhinitis perennially, then an allergic manifestation of the gastrointestinal tract. After surgery to the nose, asthma followed. These manifestations completely cleared when contact to these allergens was interrupted.

STATUS ASTHMATICUS

This special group of intractable asthmatics can be considered as a subdivision of Group II which is comprised of those cases in which infections in the paranasal sinuses and bronchial tubes are present and skin tests to inhalants and foods are negative. However, any asthmatic patient may lapse into a state of persistent uncontrollable wheezing, cough and dyspnea. Frequently the injudicious use of epinephrine by inhalation or injection, and of ephedrine products, may result in a status asthmaticus. These patients are thought to be epinephrine fast but it is questionable whether or not epinephrine fails to act. Its use may fail to relieve dyspnea when tenacious bronchial plugs cannot be dislodged.

Most deaths from asthma are in status asthmaticus. They usually occur between ages 40 and 60 and approximately 40 per cent of the patients who die have had the disease for less than five years, 60 per cent for less than two years. There is a period of intense dyspnea, marked wheezing and an associated outpouring of an extremely tenacious viscid secretion which produces an inelastic, relatively indistensible lung and diminishes the vital capacity. Massive pulmonary collapse following complete bronchial obstruction has been described. This intractable asthmatic condition may be prolonged to several days or a week, when it terminates with an abundant expectoration. Death may occur from exhaustion or heart failure. Fever of 101° to 102° F. may be present on the third day and may continue for four or five days or until the attack is over. Pulmonary consolidation with physical signs of pneumonia may complicate the picture.

When intractable status asthmaticus occurs, the patient no longer responds to epinephrine or other drugs that relieve asthma. One of the best measures to use in this condition is the inhalation of oxygen 20 per cent and helium 80 per cent by means of the B.L.B. mask. The low specific gravity of this mixture allows the gas to penetrate through the obstructed bronchi. Epinephrine if already given previously without effect should be discontinued. Helium and oxygen should be inhaled for as long as three or four hours at one time, if necessary, and

may be continued for a longer period if relief does not ensue. Periodic inhalations lasting one to two hours may be necessary for two to five days to relieve a severe attack. Once the attack is brought under control, epinephrine in oil 1:500 intramuscularly may be given for the milder wheezing which may recur. Complete anesthesia with the use of ether inhalation has been tried with success in breaking up a severe attack of intractable asthma. A mixture of equal parts of ether in olive oil, 150 cc. to 200 cc. as a retention enema, will often stop the attack. Sedation with chloral hydrate by mouth or rectally, paraldehyde, phenobarbital or nembutal is useful in stopping the attack.

Morphine should not be used since it increases bronchiolar constriction and depresses the medullary cough and respiratory centers. These patients became dehydrated rapidly, and fluids, as 5 or 10 per cent glucose in normal saline solution, 1000 cc. intravenously every twelve hours, are a valuable adjunct. Glucose is essential to replace the liver glycogen stores which have been depleted by epinephrine. Should signs of right heart failure supervene, digitalis should be given in the form of digifolin 0.1 gm. (1½ grains) four times a day for four days or one of the digitoxin preparations as crystodigin, 0.2 mg. every four hours for six doses, and this will usually suffice to digitalize the average patient. When wheezing and dyspnea are subsiding, potassium iodide 0.65 to 1 gm. (10 to 15 grains) with the addition of apomorphine hydrochloride 2.5 to 3 mg. ($\frac{1}{24}$ to $\frac{1}{20}$ grain) and tincture of lobelia 0.65 to 1 cc. (10 to 15 minims) is useful in aiding the expectoration of the viscid, tenacious sputum.

It may be necessary to resort to bronchoscopy and aspiration of the tenacious sputum and bronchial plugs. My personal experience with bronchoscopy has been exceptionally successful in several patients with intractable asthma. Following the aspiration of considerable viscid secretion and plugs, the dyspnea and wheezing rapidly subsided after all other measures had failed. It is, therefore, not wise to wait too long should other methods fail, because severe exhaustion or heart failure may later contraindicate the use of this often life-saving treatment.

Case V.—Mrs. L. J., aged 59, was perfectly well until she contracted a cold around Thanksgiving Day of 1944, when she noticed a distressing cough with shortness of breath, wheezing and nasal congestion. She had never had hay fever or asthma previously and she had a negative family history of allergy. Physical examination revealed an obese female who was coughing incessantly. There were large hypertrophied tonsils, nasal polyps on the left, a few sibilant and sonorous rales along the larger bronchi. Blood pressure was 138/100. The rest of the physical examination was negative. All intradermal skin tests were negative. I referred her to an otolaryngologist because of the nasal polyps and for an investigation of the sinuses. The report was pansinusitis in addition to the nasal polyps, and he advised removal of the polyps in order to establish better drainage. The polyps were removed and almost immediately thereafter the patient went into status asthmaticus. In spite of the use of helium and oxygen and sedation, the course

became progressively more severe and it was decided to call in a bronchoscopist. At bronchoscopy, an extremely viscid, tenacious purulent exudate with sticky plugs was aspirated. Relief of the status asthmaticus was almost instantaneous, and the slighter wheezing which persisted was easily controlled by epinephrine in oil. An autogenous vaccine was made from the aspirated exudate and a course of injections was given which was followed by considerable improvement. She was also given potassium iodide, 1 gm. (15 grains) three times a day, for a considerable period of time.

This asthma was undoubtedly an allergic reaction to the products of her own infections in the sinuses and bronchi. It should also be pointed out that bronchoscopy was life-saving in this case.

TREATMENT OF THE ACUTE ATTACK OF ASTHMA

Epinephrine hydrochloride 1:1000, 0.2 to 0.35 cc. (3 to 5 minims) subcutaneously, is the best for prompt relief of wheezing. This dose may be repeated every twenty to thirty minutes until relief is afforded. Larger doses produce toxic effects such as marked pallor, weakness and rapid heart. When the wheezing and difficult breathing are somewhat relieved, ephedrine 25 mg. (⅜ grain) with or without an added sedative such as phenobarbital 16 mg. (¼ grain) or nembutal 32 mg. (½ grain) may be prescribed by mouth every three to four hours to maintain relief. Epinephrine 1:100 by inhalation used in a glass vaporizer often affords marked relief. Children tolerate ephedrine very well and one-half the adult dose can be given to children from 5 to 10 years of age. Care must be exercised in giving ephedrine to older people because it may produce a congestion in an already hypertrophied prostate and result in difficulty in urination or complete obstruction. If this symptom appears the use of ephedrine should be stopped at once and a drug such as propadrine hydrochloride in 25 or 50 mg. (⅜ or ¾ grain) capsules should be substituted. Potassium iodide, 0.65 to 1 gm. (10 to 15 grains) well diluted in milk or water, should be given between attacks for a long period of time. In children, syrup of hydriodic acid, 0.65 to 1 cc. (10 to 15 minims) well diluted in fruit juice, milk or water, is highly beneficial and can be given for long periods of time. Expectorants such as ammonium chloride 0.65 to 1 gm. (10 to 15 grains), three or four times a day, tincture of lobelia 0.65 to 1 cc. (10 to 15 minims), apomorphine hydrochloride 2.5 or 3 mg. ($\frac{1}{24}$ or $\frac{1}{20}$ grains) and ammonium carbonate 0.33 gm. (5 grains) can be used to liquefy bronchial secretions. Excessive cough not accompanied by expectoration or wheezing may be controlled by the use of hycodan bitartrate 5 mg. every four to six hours. As previously mentioned, this preparation is nonhabit-forming and is far superior to codeine. Tinctura opii camphorata in 0.65 to 1 cc. (10 to 15 minim) doses also is useful as a sedative expectorant.

Morphine and codeine are contraindicated in asthma because of the depression of the respiratory center and cough reflex which these drugs produce.

ANTIHISTAMINIC DRUGS

Benadryl, pyribenzamine, antergan and several other drugs of this group that are now being tried experimentally are not especially helpful in asthma. While their action is thought to be due to the displacement of histamine from the tissues, they have little if any antispasmodic effect on the bronchial tubes. Hydryllin (Searle & Co.), a combination of benadryl 25 mg. and aminophylline 100 mg., given three or four times a day does relieve some patients of asthma. I have found it more helpful than any of the antihistaminic drugs used alone. A combination of benadryl 50 or 100 mg. with ephedrine 25 or 50 mg. (⅜ or ¾ grain) is also beneficial in relieving an asthmatic paroxysm. The sedative action of benadryl plus the relaxing bronchiolar effect of ephedrine has been of more benefit in asthma than any of the other drugs used in my experience.

Other drugs that were previously used in asthma, particularly belladonna, are mentioned here only to be condemned. Belladonna in any form aids in thickening bronchial secretions and making the expulsion of the plugs and already tenacious sputum more difficult. By its drying effect on the mucous membrane of the throat and bronchi, the cough is made worse and increased cough results in increased bronchiolar constriction with wheezing. Dilaudid 1.4 to 2.8 mg. (1/48 to 1/24 grain), pantopan 5 to 10 mg. (1/12 to 1/6 grain) and demerol hydrochloride 50 mg. by mouth may be added to expectorants in order to control severe coughing paroxysms without the danger of depressing the respiratory center.

RESULTS OF TREATMENT

Asthma can be successfully controlled and eliminated if the physician identifies the primary antigenic factors and eliminates them entirely from the patient's contact.

If the excitants such as pollens, dusts, orris root, animal danders and molds cannot be avoided as inhalants, specific hyposensitization therapy is usually successful.

The results in patients with asthma due to foods are excellent provided the latter are properly identified and completely eliminated from the diet.

The more chronic the asthma becomes, the more difficult it is to obtain successful results owing to the inability to control the pathological processes which result after persistent and repeated attacks.

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FOOD ALLERGY

THERON G. RANDOLPH, M.D.*

INASMUCH as the very existence of food allergy depends upon the demonstration of a cause-and-effect relationship between the ingestion of a specific food and the production or accentuation of allergic symptoms, it follows that diagnostic measures for the detection of food sensitivity should be concerned primarily with observations of the effects produced by the experimental feeding of particular foods. This is accomplished to best advantage by returning a previously eliminated food to the diet under experimentally controlled conditions in the patient favoring the production of maximum symptoms and under environmental circumstances permitting the most accurate measurement of this symptom response.

In the presence of these qualifying conditions, current clinical sensitivity cannot be inferred by the patient's suspicion of specific foods, by the occurrence of positive skin tests with food extracts, or even by the relief of symptoms following the elimination of one or more foods. Conversely, food allergy cannot be ruled out by the failure of a patient to suspect it, by negative skin tests or by the failure to respond to one or more particular elimination diets.

The demonstration of a cause-and-effect relationship between the ingestion of a specific food and the production or accentuation of allergic symptoms is not a simple task, either for the patient or for the physician. The patient must be willing and able to follow precise dietary instructions—a difficult assignment in view of the complexities of modern commercially prepared foods, traditional eating habits, and the ineptitude (or, perhaps, the inexperience) of individuals in submitting to controlled conditions affecting their food intake. The physician, even though trained in this field and accustomed to its minutiae, is also at a disadvantage in observing the effects of the ingestion of a given food for he is usually called upon to diagnose these cases specifically in the presence of chronic uncontrolled symptoms most commonly resulting from sensitivity to multiple foods and multiple inhalants.

The specific diagnosis of food allergy in a given case challenges the powers of observation of both the doctor and the patient. The physician first of all must decide whether a given individual may be having allergic symptoms; this requires a workable knowledge of the clinical manifestations that may be of allergic origin.

Aided by a grant from Swift and Company for the Study of Food Allergy.

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The second requirement for the physician conducting the allergic study is to appraise the existence of inhalant allergy. If present this should be controlled by adequate measures prior to and throughout the period of specific food diagnosis, for otherwise the persistence of inhalant symptoms may interfere with observations of the patient during food testing.

The physician's third obligation is to proceed with the food investigation in an orderly fashion by means of technics which will reveal most accurately the clinical effects of individual foods and to determine at an early stage of the diagnostic study whether the patient under observation has a high or a low inherent tolerance for foods. As will subsequently be brought out, the patient who already has a widespread food allergy problem should not be placed on a highly restricted elimination diet because of the ease with which sensitivity may spread to substituted foods ingested in oft-repeated feedings. Therefore, the physician should have a clear understanding of the importance of maintaining existing tolerance for given foods in addition to the desirability of detecting the presence of intolerance to others.

Last and most important, the physician must know precisely what happens following the experimental feeding of individual foods; this means that clinical observations must be accurately made, recorded and interpreted. In reviewing the clinical evidence in respect to the food intake and symptoms, he must constantly be on guard to make factual deductions rather than conclusions falling under the heading of the common error of logic known as "Post hoc, ergo, propter hoc," of which the following is an example: It is common knowledge that roosters crow early in the morning and that dawn occurs shortly thereafter; therefore, it dawns because the cocks crow!

The physician may be aided tremendously in this task of observation by training his office personnel and his patients to become good observers; this, of course, includes the accurate and immediate recording of all relevant data. The patient aids in this process by keeping a food diary and symptom record showing the exact foods eaten and the circumstances associated with the precipitation or sharp accentuation of various symptoms. It is obviously important that the patient be told how to keep a diary of this type and, preferably, that printed forms be furnished for the purpose.

It should be quite obvious from this preamble that the specific diagnosis of food allergy is a joint endeavor and, as such, should be undertaken *with* the patient rather than on, or even for, the patient.

MISCONCEPTIONS REGARDING FOOD ALLERGY

Differences of opinion regarding the recognition of food allergy seem to result from the perpetuation of several misconceptions. First, there is the impression that food sensitivity is concerned primarily

with children, whereas, actually, it is at least as common and usually more complicated in adults, in view of the multiplicity of foods involved and the greater interrelationship with inhalant allergy.

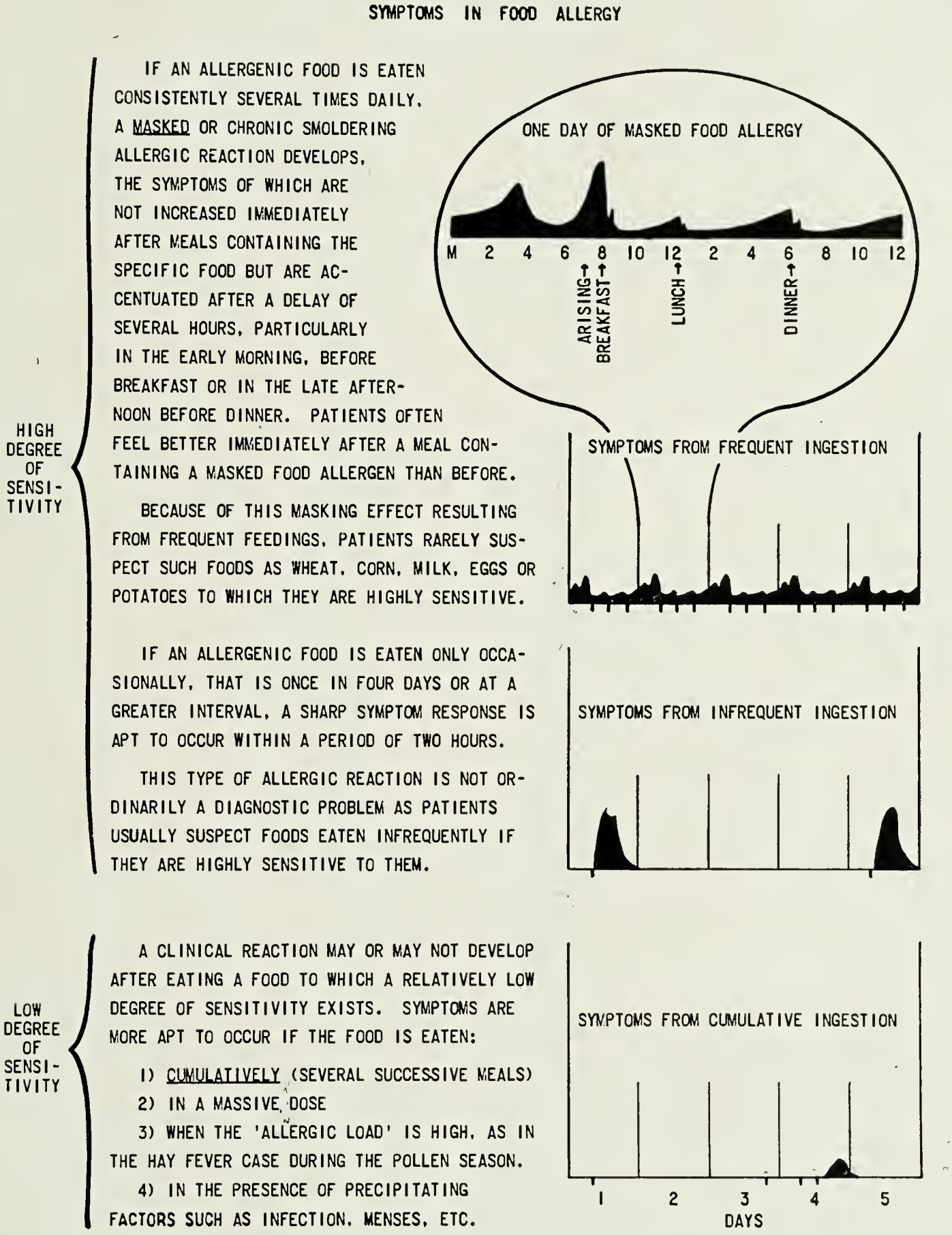
SYMPTOMS IN FOOD ALLERGY
HIGH DEGREE OF SENSITIVITY
IF AN ALLERGENIC FOOD IS EATEN CONSISTENTLY SEVERAL TIMES DAILY, A MASKED OR CHRONIC SMOLDERING ALLERGIC REACTION DEVELOPS, THE SYMPTOMS OF WHICH ARE NOT INCREASED IMMEDIATELY AFTER MEALS CONTAINING THE SPECIFIC FOOD BUT ARE ACCENTUATED AFTER A DELAY OF SEVERAL HOURS, PARTICULARLY IN THE EARLY MORNING, BEFORE BREAKFAST OR IN THE LATE AFTERNOON BEFORE DINNER. PATIENTS OFTEN FEEL BETTER IMMEDIATELY AFTER A MEAL CONTAINING A MASKED FOOD ALLERGEN THAN BEFORE.
BECAUSE OF THIS MASKING EFFECT RESULTING FROM FREQUENT FEEDINGS, PATIENTS RARELY SUSPECT SUCH FOODS AS WHEAT, CORN, MILK, EGGS OR POTATOES TO WHICH THEY ARE HIGHLY SENSITIVE.
ONE DAY OF MASKED FOOD ALLERGY
M 2 4 6 8 10 12 2 4 6 8 10 12
ARISING
BREAKFAST
LUNCH
DINNER
SYMPTOMS FROM FREQUENT INGESTION
IF AN ALLERGENIC FOOD IS EATEN ONLY OCCASIONALLY, THAT IS ONCE IN FOUR DAYS OR AT A GREATER INTERVAL, A SHARP SYMPTOM RESPONSE IS APT TO OCCUR WITHIN A PERIOD OF TWO HOURS.
THIS TYPE OF ALLERGIC REACTION IS NOT ORDINARILY A DIAGNOSTIC PROBLEM AS PATIENTS USUALLY SUSPECT FOODS EATEN INFREQUENTLY IF THEY ARE HIGHLY SENSITIVE TO THEM.
SYMPTOMS FROM INFREQUENT INGESTION
LOW DEGREE OF SENSITIVITY
A CLINICAL REACTION MAY OR MAY NOT DEVELOP AFTER EATING A FOOD TO WHICH A RELATIVELY LOW DEGREE OF SENSITIVITY EXISTS. SYMPTOMS ARE MORE APT TO OCCUR IF THE FOOD IS EATEN:
1) CUMULATIVELY (SEVERAL SUCCESSIVE MEALS)
2) IN A MASSIVE DOSE
3) WHEN THE 'ALLERGIC LOAD' IS HIGH, AS IN THE HAY FEVER CASE DURING THE POLLEN SEASON.
4) IN THE PRESENCE OF PRECIPITATING FACTORS SUCH AS INFECTION, MENSES, ETC.
SYMPTOMS FROM CUMULATIVE INGESTION
1 2 3 4 5
DAYS

Fig. 54.

Second, there is the prevalent notion that patients will be able to detect the existence of sensitivity to an article of the diet. This is commonly true with foods eaten occasionally but a patient rarely suspects

sensitivity to a food ingested at frequent intervals. Actually, the greatest single shortcoming of the allergy history is that it fails to indicate sensitivity to the most important foods in the diet. This is attributable to the masking effect of symptoms so commonly resulting from the oft-repeated use of a given food allergen. This fundamental concept, developed by Rinkel[1] and briefly outlined in Figure 54, aids in understanding many important points in the allergy history.

The third misconception in reference to food allergy deals with the literal interpretation of skin tests with food extracts. The false impression that skin tests with foods afford accurate diagnostic information apparently originated in part from analogy. That skin tests with inhalant allergens are highly reliable was common knowledge, and it was hoped that food sensitivity might be as readily detected. However, when skin test results are checked in cases carefully diagnosed on a clinical basis, both false positive and false negative reactions are seen to occur with such frequency as to cast serious doubt on the ability of cutaneous or intracutaneous tests to indicate current specific sensitivity. Although positive skin tests with food extracts are occasionally associated with current clinical reactions, when the same foods are tested under correct experimental conditions it becomes apparent that skin tests with foods are so unreliable that a diagnostic diet based on their results is apt to be more misleading than helpful. Such an approach to the diagnosis of food allergy is often disadvantageous in that it utilizes the patient's most valuable period of cooperation in following a restricted diet, it being the exceptional patient who will follow through cooperatively on some subsequent and more fundamentally sound diagnostic plan. I am of the opinion that skin tests with food extracts, mechanically performed and literally interpreted, have done more to retard than to promote general acceptance by the profession of the full rôle of food allergy in clinical medicine. For the reasons given, I have not performed cutaneous or intracutaneous skin tests with the major food allergens during the past five years.

The assumption that food allergy deals primarily with sensitivity to wheat, milk and eggs, or that certain other foods may be safely included on elimination diets is also erroneous. In cases diagnosed on a clinical basis corn is the most commonly encountered food allergen, corn sensitivity being slightly higher in incidence than sensitivity to wheat or milk and significantly more frequent than egg or potato allergy. This statement is based on the result of a recent and as yet unpublished survery of 200 consecutive new cases of suspected food allergy studied by means of individual food tests with corn, wheat, milk and eggs. Unfortunately, several widely used elimination diets fail to eliminate corn completely. The continuation of even small amounts of corn starch or corn sugar (glucose, dextrose and cellulose) in an elimination diet will perpetuate symptoms in a patient highly

sensitive to corn.* It should be emphasized that any article of the diet may be one of the causes of acute or chronic allergic symptoms.

MANIFESTATIONS OF FOOD ALLERGY

Although foods may be the sole or contributing cause of any allergic manifestation, the combination of food and inhalant sensitivity is a much more common occurrence. Inhalant sensitivity plays the dominant role in seasonal rhinitis or asthma, which usually results from pollen or fungus sensitivity when symptoms are limited to the summer months, and from sensitivity to house dust or epidermals when symptoms are present primarily in the winter. Concomitant food sensitivity which manifests itself only during the season of inhalant sensitivity or in association with certain thermal variations must always be considered as a possible contributing factor in patients who have not responded satisfactorily to otherwise adequate diagnosis and therapy of inhalant sensitivity.

Food sensitivity is the most common etiologic factor in cases of perennial allergic rhinitis and perennial bronchial asthma, irrespective of the age of the patient. It is the most common mechanism in the specific etiology of atopic dermatitis and gastrointestinal allergy. The latter appears to be the most common clinical reaction of food sensitivity. Among various other specific and nonspecific factors, food sensivity must always be given etiological consideration in cases of acute or chronic urticaria.

In addition, food allergy is frequently the cause of various other symptoms, many of which are not investigated regularly from this standpoint. One of the most commonly encountered is the allergic headache which may be of any descriptive type, including so-called "histaminic cephalalgia." The clinical syndrome which might be called the fatigue picture of allergic origin is also a very common manifestation of food sensitivity;[3, 4] this is characterized by a peculiar type of fatigue and listlessness, and, in many instances, by muscle drawing and aching (particularly in the nuchal region, the lower back, and the hamstring and calf muscles), irritability, tenseness (often referred to by the patient as nervousness) and sometimes by mental depression which in extreme cases may reach the point of melancholia and abnormalities of behavior. It is a common error to assume that all symptoms of this type occurring in the allergic person, in the absence of positive physical findings, are manifestations of psychosomatic disease.

Various minor clinical manifestations of food sensitivity affecting the

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* For instance the present form of the Rowe Elimination Diets[2] includes baking powder containing corn starch. Certain brands of bacon, white vinegar and commercially prepared soybean substitutes for milk, permitted on some of those diets, also contain corn sugar. Even the highly restricted diet of rice, lamb and pears would contain corn sugar if standard brands of commercially canned pears were used.

genitourinary tract and the hemopoietic and nervous systems cannot be discussed in the space allotted.

THE DIAGNOSIS OF SPECIFIC FOOD ALLERGY

The methods employed in the specific diagnosis of food allergy are identical whether the patient happens to have one or another of the various clinical manifestations of allergic disease.

Because of the frequent coexistence of inhalant and food allergy, inhalant sensitivity should be investigated first. If found to exist, it should be controlled by specific avoidance and treatment both as a prerequisite for initiating diagnostic studies for food sensitivity and as a necessity throughout the course of such observations. In certain cases, this program will obviate the necessity for studying food allergy. In other instances, where investigation of a food allergy is indicated, it will minimize inhalant symptoms during the period one is observing the cause-and-effect relationship of specific foods to allergic symptoms.

Inasmuch as the objectives in the diagnosis of food allergy are, first, to determine the extent to which the diet is involved by the current allergic process and, second, to determine the degree of sensitivity existing to particular foods, one must therefore employ a diagnostic approach which measures most accurately the clinical allergic reaction to individual foods.

In this connection one should not overemphasize the importance of the patient's impressions regarding the presence or absence of food allergy or the existence of specific sensitization to particular foods. The most highly allergic person is commonly the most vehement in denying food allergy, and if an individual claims that there is a common food he is certain that he can eat because he invariably feels better afterward, this food should be the first to be suspected by his doctor (see description of masked food allergy in Figure 54).

In spite of the shortcoming of the specific food allergy history, the following items are worth recording: (1) suspected foods, including the evidence for such claims; (2) food dislikes and reasons for such; (3) the evaluation of childhood dietary factors in relation to illnesses; (4) the influence on the patient's symptoms of previous dietary manipulation of any type; and (5) the quantitative food intake history. The last is the most important and should include the number of times per day or per week that the major food allergens are eaten. A useful form for this purpose is shown on the left side of Figure 55. The right side of this form serves as a convenient record for subsequent changes in the diet.

In the event that allergic symptoms are occurring in intermittent attacks at an interval of once a week or less frequently and the patient is entirely symptom-free between attacks, helpful diagnostic information may be obtained from details of the recent history and a carefully recorded food diary covering a period of several episodes. As a rule,

however, this type of patient does not consult a physician nearly as frequently as does the individual having chronic daily symp-

FOOD ALLERGY RECORD SHEET

NAME _____ NO. _____ DATE _____

MEALS HOME _____ MEALS OUT _____ CARRIES LUNCH _____

QUANTITATIVE FOOD INTAKE HISTORY				SUMMARY OF DIETARY CHANGES
FOODS	PER DAY	PER WK.	SUS-PECTS	
APPLE				
BANANA				
BARLEY, MALT				
BEANS				
BEEF, VEAL				
BEETS				
CABBAGE				
CARROTS				
CELERY				
CHICKEN				
CHOCOLATE				
CORN				
EGGS				
FISH				
GRAPEFRUIT				
LAMB				
LEMON				
LETTUCE				
MILK				
ICE CREAM				
OATMEAL				
ORANGE				
PEACH				
PEANUT				
PEAR				
PEAS				
PINEAPPLE				
PORK				
POTATO				
RICE				
RYE				
SWEET POTATO				
TOMATO				
WHEAT, BREAD OR ROLLS				
CEREAL				
MACARONI, SPAGHETTI, ETC.				
PIES, CAKES, COOKIES, ETC.				
YEAST				
DRINKS, ETC.		CALCIUM VITAMIN		
COFFEE				
TEA				
SOFT DRINKS				
CANDY				
GUM				
BEER				
LIQUOR				
	BASIC DIETS	CWRMEL PT CWRMEL F CWOMEL PT GME T GME F		

Fig. 55.

toms. From the foregoing, it should be apparent that the latter group includes the patients having such constitutional symptoms as the fa-

tigue syndrome of allergic origin (otherwise unexplained on an organic basis) existing between more classical allergic reactions.

Aside from the history, the diagnostic approach for the detection of specific food allergy in the chronic case may be considered under several headings, the aim in each instance being to prescribe an initial diagnostic diet which will avoid that individual's allergenic foods as simply and as harmlessly as possible.

The method of choice and the one most accurate scientifically is to perform individual food tests with the six or eight foods the patient eats most frequently. In the event that only one or two such tests are associated with the production or the accentuation of allergic symptoms, the patient may be assumed to have a narrow base of sensitivity; this, in turn, is usually associated with a high inherent tolerance for foods. As further explained in Figure 56, this patient is not apt to acquire sensitivity to the oft-repeated ingestion of currently tolerated foods and may be placed, with considerable safety as far as the long range point of view is concerned, on a diagnostic diet of short duration restricted to a group of compatible foods determined from the result of several individual food tests.

In the event that 50 per cent or more of the first six or eight common foods tested individually are associated with the production of allergic symptoms, a highly restricted elimination diet including only test-negative foods is not indicated, for the presence of a wide base of sensitivity is usually associated with a low inherent tolerance for foods, and a sharply restricted diet, although of only a few days' duration, may do irreparable harm. The diagnosis and treatment of this type of case, the most difficult problem encountered in clinical allergy, cannot be rigidly separated; the management of this clinical situation will be considered later.

The current technic of the individual food test, originated by Rinkel[5] and confirmed by Randolph and Rawling,[6] consists, briefly, of the following: A food, previously eaten regularly, is completely eliminated for a period of four days prior to test feeding.* On the fifth day the patient arrives in the office in a fasting condition and rests for thirty minutes, during which period a careful record is kept of the incidence per unit of time of sneezing, coughing and all other allergic symptoms. The subject is then fed a large serving of the food in question and similarly observed for another hour. In the event that diagnostic symptoms have not developed, a second feeding is given at the end of an hour and clinical observations are continued for an additional half hour. Total leukocyte counts are performed prior to and at twenty, forty and sixty minutes after the first feeding.

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* It obviously is essential to provide the patient with detailed instructions on how to avoid the food in question, including a sheet of instructions of the common sources in the diet. This information will be available in a separate publication[7] or as part of a monograph on food allergy[8] soon to be published.

TYPES OF FOOD ALLERGY
BASED ON THE EXTENT OF INVOLVEMENT OF THE DIET

I. NARROW BASE OF SENSITIVITY, HIGH INHERENT TOLERANCE FOR FOODS

A NARROW BASE OF SENSITIVITY EXISTS IF A PATIENT REACTS WITH SYMPTOMS ON INDIVIDUAL FOOD TESTS WITH ONLY ONE OR TWO OF THE FIRST FOUR OR FIVE MAJOR ALLERGENIC FOODS LISTED BELOW.

RESTRICTED DIAGNOSTIC DIETS MAY BE EMPLOYED IN THIS TYPE OF CASE AND THE RESULTS OF SPECIFIC AVOIDANCE ARE USUALLY GOOD. NOT ONLY MAY THE OFFENDING FOOD BE READILY AVOIDED BUT SENSITIVITY IS NOT APT TO SPREAD TO OTHER MAJOR OR SUBSTITUTED FOODS.

II. WIDE BASE OF SENSITIVITY, LOW INHERENT TOLERANCE FOR FOODS

A WIDE BASE OF SENSITIVITY EXISTS IF ONE REACTS WITH SYMPTOMS ON INDIVIDUAL FOOD TESTS WITH MORE THAN HALF OF THE TESTS PERFORMED.

THIS TYPE OF CASE SHOULD NOT BE PLACED ON A HIGHLY RESTRICTED DIET BECAUSE OF THE EASE WITH WHICH SENSITIVITY MAY SPREAD TO SUBSTITUTED FOODS. SOME PATIENTS WITH AN EXCEEDINGLY LOW INHERENT TOLERANCE FOR FOODS APPEAR ABLE TO BECOME SENSITIZED TO ANY ARTICLE OF THE DIET IF IT IS USED FREQUENTLY AND CONSISTENTLY. PATIENTS WITH SUCH POTENTIALITIES ARE BEST CONTROLLED BY EATING A WIDE VARIETY OF TOLERATED FOODS, ROTATING THEM IN THE DIET AND AVOIDING THE FREQUENT USE OF FOODS BOTANICALLY RELATED TO KNOWN ALLERGIC OFFENDERS.

THE ORDER OF INCIDENCE OF FOODS CAUSING MASKED OR CUMULATIVE ALLERGIC REACTIONS

THE INCIDENCE OF SENSITIVITY TO CORN, WHEAT, MILK AND EGGS WAS DETERMINED FROM A SURVEY OF 200 CONSECUTIVE CASES STUDIED FOR FOOD ALLERGY BY DIRECT METHODS, I.E. BY MEANS OF INDIVIDUAL FOOD TESTS WITH THOSE FOUR FOODS AND SUBSEQUENT CLINICAL FOLLOW UP. THE RELATIVE INCIDENCE OF SENSITIVITY TO OTHER FOODS IS ESTIMATED FROM CLINICAL EXPERIENCE.

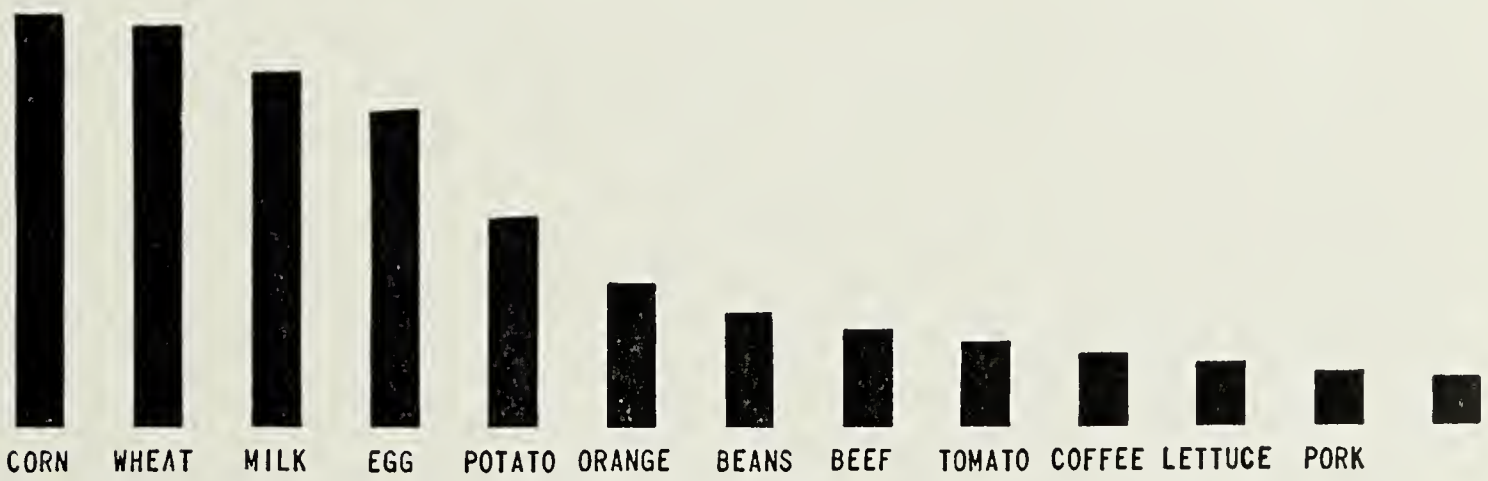


Fig. 56.

The technic in which the specific food is avoided for four days prior to experimental feeding has a decided advantage over the leukopenic index as described by Vaughan,[9, 10] in that it allows the patient to re-

cover from the masked symptoms resulting from the frequent ingestion of that particular food (as illustrated in the upper parts of Figure 54). The formerly masked food then acts as it would if taken at infrequent intervals (see mid part of Figure 54). In the event of a high degree of sensitivity, a prompt and unmistakable symptom reaction may be expected (a doubling of the incidence or of the severity of symptoms is regarded as diagnostic). This demonstration of a clear-cut cause-and-effect relationship between the experimental feeding of particular foods and induced symptoms is likely to insure a more satisfactory degree of patient cooperation in following the initial diagnostic diet than is ordinarily obtained by other means of arriving at the first diet.

In the presence of lower degrees of sensitivity the onset of symptoms is apt to be more delayed, frequently coming on after the patient leaves the office. In the absence of symptoms, a postprandial leukopenia of 10 per cent or greater occurring in any of the postingestive counts as compared with the basal determination or with a subsequent postingestive leukocyte count is presumptive evidence of sensitivity. This leukocyte variation in the absence of symptoms commonly indicates a cumulative offender; these points have been carefully checked in a large series of cases and, in connection with the following statement, constitute the chief reasons for performing serial total leukocyte determinations. I agree with Rinkel[5] that the presence of a trajectory curve of leukocytosis is evidence that the food in question is currently tolerated, and that in the hands of the physician with a workable knowledge of the dynamic nature and mechanism of food allergy this test procedure is 90 per cent reliable as a diagnostic method in detecting specific food sensitivity.

In summary, then, the performance of individual food tests with the major potential allergens of the diet, at an early stage of the diagnostic study, gives evidence meeting the objectives of the food allergy investigation, namely: (1) information concerning the degree of sensitization existing to the various major foods; and (2) indication of the extent to which the diet is involved by the sensitization process. These factors constitute fundamental points in the classification of food allergy and determine the dietary approach from this juncture forward.

An alternative approach to the initial diagnostic diet, but one which includes considerably more guesswork, is the performance of individual food tests with three or four major articles of the diet, usually choosing between corn, wheat, milk, eggs and potatoes. From the results of these tests and the details of the food history, a basic type of elimination diet is prescribed to which are added two or more major foods found compatible as checked by the individual food test technic. The author has found a series of five basic diagnostic diets of use in this connection, each to be prescribed with four sheets of recipes. These diets and their accompanying recipe sheets are named in terms of the major foods eliminated, i.e., the cereal grains, corn, wheat, rye, oats, milk, eggs, legumes, potatoes, tomatoes and fruit, as indicated in Figure 57. It will be noted that each diet eliminates the first four major foods as listed in the order of incidence of sensitivity, namely corn, wheat, milk and eggs. Details of these diets will be published elsewhere.[11]

If, however, 50 per cent or more of the first three or four individual food tests show incompatibility, this is presumptive evidence of a low inherent tolerance for foods. At this point an additional group of three or four food tests is performed which places the patient in the category initially described, and decisions as to the future course of events are based on the same evidence as previously outlined.

The third diagnostic approach, listed in the order of its desirability in the detection of specific food allergy, is the prescription of one of the aforementioned diets chosen solely on the basis of the patient's food history. This entails a pure guess as to the possible food allergens in a given case and necessitates exclusion of at least the first five foods listed in the order of the incidence of sensitivity (see lower part of Fig. 56). There is a moderate to good chance that one of these diets will relieve current allergic symptoms, the keystone to the diagnosis of specific food sensitivity. Nevertheless, should the patient happen to have a low inherent tolerance for foods, he might develop sensitization to substituted foods used repeatedly on this diet before he recovered from the effects of the specific allergens that were eliminated. Should the initial basic diet have represented a poor guess and included one or more active food allergens, not only will chronic symptoms

BASIC DIETS

RECIPE SHEETS FOR USE WITH BASIC DIETS	CWRMEL PT	CWRMEL F	CWOMEL PT	GME T	GME F
GMEL PTF	X	X	X	X	X
GMEL PT	X		X	X	
GMEL F		X			X
GME TF				X	X
GME T				X	
GME F					X
CWRMEL PTF	X	X	X		
CWRMEL PT	X				
CWRMEL F		X			
CWOMEL PT			X		

ABBREVIATIONS USED

C : CORN
W : WHEAT
R : RYE
O : OATS
M : MILK
E : EGGS
L : LEGUMES
P : POTATOES
T : TOMATOES
F : FRUIT
G : GRAINS, C,W,R,O, BARLEY AND RICE

Fig. 57.

continue but there is the additional hazard that the patient may also have acquired new sensitivities from the use of this diet, thus gaining nothing and losing much. Under such circumstances, which are not uncommon, a part of the loss is the fact that the concept of food allergy as a cause of symptoms has been discredited in the minds of both the physician and the patient. This diagnostic approach commonly backfires, and when it does one might characterize it in retrospect by the succinct phrase of "the wrong guess on the wronged patient." Only one thing is worse for the far-advanced case of food sensitivity, that is several repeated wrong guesses (the prescription of serial highly restricted elimination diets).

An even less desirable approach to the initial diagnostic diet, an approach which is least objective and least scientific, is a restricted diet based on skin test evidence. For reasons given, this program cannot be recommended.

Another approach to the problem is to place a patient on a diet of hydrolyzed proteins. To date this has not developed into a satisfactory program in view of the unpalatability of such mixtures, the fact that commercially available hydrolysates derived from milk, beef or yeast may not be completely nonallergenic in respect to the source materials, and the distinct possibility that an allergic reaction might develop to such a product in its own right when it is used as the sole source of nutrition.

In the event that a restricted diet is prescribed, *how long should it be followed?* Patients should not be maintained on a highly restricted dietary program, either limited to compatible foods as determined from individual food tests or as a result of a basic type of elimination diet, for periods longer than a week to ten days, regardless of whether or not symptoms have been relieved. If the diet is correct one will usually observe some evidence of improvement by the end of two or three days, with sustained improvement after four or five days.

How and when should omitted foods be returned to the diet after the patient's chronic symptoms have been relieved? From a diagnostic standpoint (the object being to produce allergic symptoms), the major avoided foods may be reintroduced after a three or four day symptom-free period; they are added in cumulative feedings one at a time in an approximate relationship to the length of the period each has been avoided. If a food has been omitted for only a week it is readmitted to the diet three times daily for a single day. If symptoms have not been reproduced or accentuated by the following morning, one may assume that specific sensitivity of a high degree does not exist and another food may be added similarly. If a food has been eliminated for over a week but less than two weeks, it should be returned to the diet twice daily for a two day period.

If symptoms are accentuated following the reintroduction of a particular food, one should remove it from the diet and wait until the symptoms have at least started to subside before making another addition. If the reaction is doubtful after cumulative ingestion the food in question should be returned again after four more days of avoidance.

What should one do in the event the initial diagnostic diet fails to relieve chronic symptoms? This is difficult to answer precisely. If the symptoms are actually due to food sensitivity, the failure to relieve them as the result of a highly restricted diet usually points to one or more of the following:

1. It may be due to the incomplete avoidance of one or more known food allergens; this error occurs with surprising frequency even though the patient is given detailed printed instructions telling precisely what to eat, as well as a list of the common sources of the eliminated foods. The unfortunate fact remains that some patients cannot be trusted to read instructions, or for some other reason do not apply the specific information at their disposal. The most satisfactory way to avoid this error is to insist that while the patient is on the initial diet all food be prepared at home and that a detailed record of everything ingested be carefully compiled. At the time of the first check-up visit the physician should check specific instructions against the actual record.

2. The initial diet may include one or more foods to which the patient is already sensitive. The greater the number of foods contained in the first diet, other than those observed under the correct conditions

of individual testing, the greater the possibility that specific allergens have not been excluded.

3. Another possibility is the development of sensitivity to a food used repeatedly in the initial diet. Although this is particularly apt to occur in the patient with a low inherent tolerance for foods, it may occur in any individual and remains the greatest single hazard associated with the correct use of a highly restricted elimination diet. This is particularly apt to occur in connection with certain foods, such as buckwheat or legumes, which seem to possess high allergenic potentials. Sensitivity to the repeated use of these foods sometimes occurs within as short a period as three or four days. Furthermore, a spread of sensitivity seems to occur readily to foods botanically related to those known to be incriminated.

4. It also appears that certain allergic manifestations associated with marked structural change in the shock organ involved respond somewhat more slowly than other allergic symptoms, even though the specific allergens are correctly eliminated. This is the exception rather than the rule.

THE TREATMENT OF FOOD ALLERGY

The therapeutic aspects of the food allergy problem may be considered to best advantage under two headings.

Cases with a Narrow Base of Sensitivity (High Inherent Tolerance for Foods).—The cardinal principle in the management of cases of food allergy having a narrow base of sensitivity is the complete and prolonged elimination of the incriminated foods. Immediately after the complete avoidance of a masked food allergen—that is, for several days to several weeks—the ingestion of a relatively small amount of a highly allergenic food may result in an acute, and sometimes violent, symptom response. Rinkel[1] describes this as the phase of hyperacute sensitization. As illustrated in Figure 58 and previously discussed, this response is used to advantage diagnostically by the performance of individual food tests after four days of avoidance.

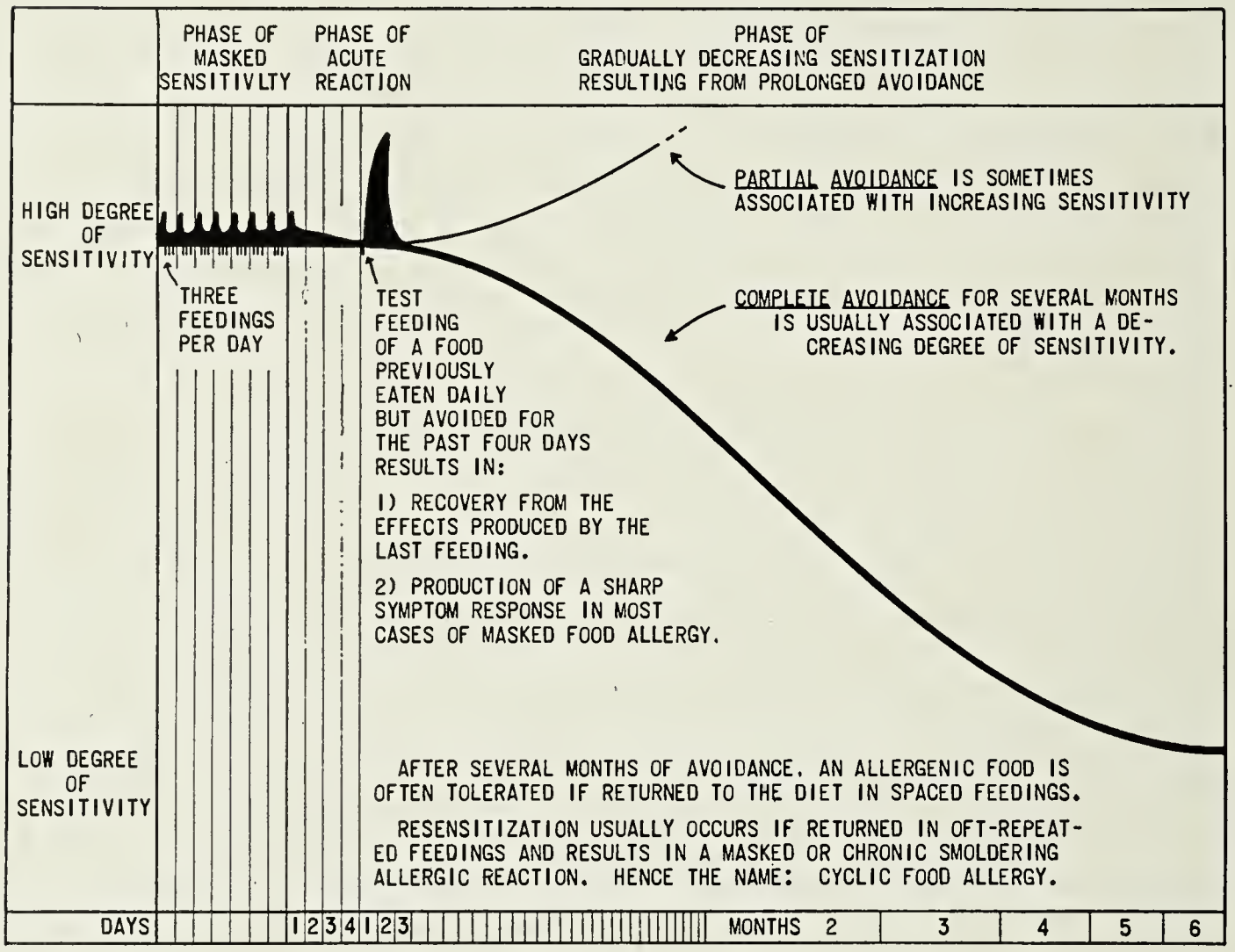
In the majority of cases of cyclic food allergy, this phase of hyperacute reaction will persist only a few weeks if the patient avoids stimulation of the specific mechanism (i.e., if he eliminates the particular food completely). In the majority of instances there ensues with the passage of additional time a progressive decrease in the degree of specific sensitization (see Figure 58), which eventually permits the reintroduction to the diet of the previously eliminated food.

The question then arises as to how and when one should reintroduce such a food? This is obviously an important point because of the desirability of maintaining the tolerance gained as a result of avoidance. From the therapeutic standpoint, the objective in returning a previously eliminated food to the diet is to avoid the production of allergic

symptoms (quite in contrast to the objective of producing allergic symptoms for the purpose of diagnosing specific sensitivity). Although we know something about how such a food should be returned, there is no concise rule to guide us as to when it is safe to try it.

TYPES OF FOOD ALLERGY
BASED ON THE RESPONSE TO SPECIFIC AVOIDANCE

I. CYCLIC FOOD ALLERGY (SENSITIVITY DECREASED BY AVOIDANCE)


PHASE OF MASKED SENSITIVITY
PHASE OF ACUTE REACTION
PHASE OF GRADUALLY DECREASING SENSITIZATION RESULTING FROM PROLONGED AVOIDANCE
HIGH DEGREE OF SENSITIVITY
LOW DEGREE OF SENSITIVITY
THREE FEEDINGS PER DAY
TEST FEEDING OF A FOOD PREVIOUSLY EATEN DAILY BUT AVOIDED FOR THE PAST FOUR DAYS RESULTS IN:
1) RECOVERY FROM THE EFFECTS PRODUCED BY THE LAST FEEDING.
2) PRODUCTION OF A SHARP SYMPTOM RESPONSE IN MOST CASES OF MASKED FOOD ALLERGY.
PARTIAL AVOIDANCE IS SOMETIMES ASSOCIATED WITH INCREASING SENSITIVITY
COMPLETE AVOIDANCE FOR SEVERAL MONTHS IS USUALLY ASSOCIATED WITH A DECREASING DEGREE OF SENSITIVITY.
AFTER SEVERAL MONTHS OF AVOIDANCE, AN ALLERGENIC FOOD IS OFTEN TOLERATED IF RETURNED TO THE DIET IN SPACED FEEDINGS.
RESENSITIZATION USUALLY OCCURS IF RETURNED IN OFT-REPEATED FEEDINGS AND RESULTS IN A MASKED OR CHRONIC SMOLDERING ALLERGIC REACTION. HENCE THE NAME: CYCLIC FOOD ALLERGY.
DAYS 1 2 3 4 1 2 3
MONTHS 2 3 4 5 6

II. FIXED FOOD ALLERGY (SENSITIVITY UNCHANGED BY AVOIDANCE)

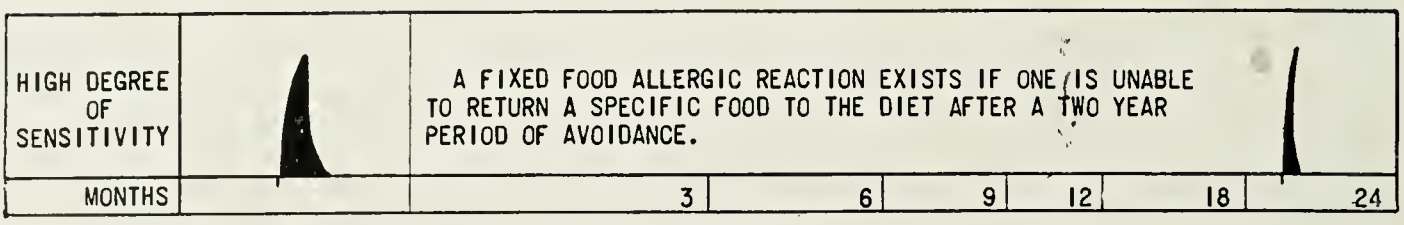

HIGH DEGREE OF SENSITIVITY
A FIXED FOOD ALLERGIC REACTION EXISTS IF ONE IS UNABLE TO RETURN A SPECIFIC FOOD TO THE DIET AFTER A TWO YEAR PERIOD OF AVOIDANCE.
MONTHS 3 6 9 12 18 24

Fig. 58.

The interval of usage of a food that can be tolerated without symptoms must be worked out gradually. It seems desirable to start by eating an average serving once in seven days. If this schedule is tolerated at the end of a month, the interval may be reduced to once in five days, and perhaps later to once in three days. Under no circum-

stances should the patient return the food indiscriminately for this is almost certain to result in resensitization. Rinkel has emphasized that the oft-repeated use of a food at this stage is very apt to be followed by the redevelopment of active sensitization usually leading again to the complete masking of symptoms. The following example serves to illustrate how thin the thread of specific tolerance may actually be:

A physician reacted with violent headache and diarrhea in the course of an individual food test with beef. In subsequent weeks the slightest amount of beef, such as beef stock in a pork gravy for instance, was sufficient to produce acute symptoms. After a period of nine months of complete avoidance, beef was returned once a week in the form of a large steak and tolerated on this schedule for a period of two months. Then while visiting away from home, he ate beef on two successive days without symptoms. The next meal of beef a week later was followed by a severe headache and diarrhea. He then avoided beef completely for three more months and for the past three months has been eating it regularly once weekly without any evidence of intolerance.

There are numerous factors which have a bearing on the question of when a food may be returned to the diet therapeutically; these include the initial degree of sensitivity as judged by the speed of onset and severity of symptoms in association with the individual food test, the duration of avoidance, the complexity of the food problem and the presence of concomitant inhalant sensitivity or other physical factors existing at various seasons. Although generalizations in this direction are hazardous in view of these variables in given cases, an initial attempt to return a food may usually be made between three months and a year after complete elimination was started.

It may be noted from Figure 58 that there might be an increase in the degree of sensitivity following the partial avoidance of a food allergen. The incomplete elimination of milk, for instance, by permitting the use of butter and milk in cooking, not only keeps sensitization active but at least in certain cases may enhance it. This unfortunate course of events is clearly illustrated in a previous case report.[12]

I agree with Rowe[2] and Rinkel[1] that one cannot be expected to develop tolerance for a food by the use of it in infinitely small amounts on a progressive schedule. Rinkel believes that any improvement that seems to follow such a plan is apt to be explained on the basis of the masking of symptoms.

There are certain cases which fail to develop any tolerance as the result of the prolonged avoidance of a specific food. Rinkel[1] describes this situation as fixed food allergy (see lower part of Fig. 58), in contrast to cyclic food allergy as described above.

Cases with a Wide Base of Sensitivity (Low Inherent Tolerance for Foods).—If the patient has a low inherent tolerance for foods, diagnostic procedures for the detection of food sensitivity may have to be continued from time to time throughout a predominately therapeutic phase of management, in view of the fact that this type of pa-

tient should not be placed on a highly restricted diagnostic diet because of the tendency for sensitivity to spread.

Although there has been no entirely satisfactory therapeutic approach to this problem, the most workable program appears to be the use of all tolerated foods on a rotating schedule, as suggested by

BIOLOGICAL CLASSIFICATION OF FOODS

MAMMALS

BEEF
VEAL
COWS MILK
BUTTER
CHEESE
GELATIN
PORK
HAM
BACON
GOAT
GOATS MILK
CHEESE
MUTTON
LAMB
VENISON
HORSE MEAT
RABBIT
SQUIRREL

AMPHIBIANS
FROG

REPTILES
TURTLE

BIRDS

CHICKEN
EGGS
TURKEY
DUCK
DUCK EGGS
GOOSE
GOOSE EGGS
GUINEA HEN
SQUAB
PHEASANT
PARTRIDGE
GROUSE

FISH

STURGEON
. CAVIAR
ANCHOVY
SARDINE
HERRING
. SHAD
SALMON
TROUT
SMELT
WHITEFISH
. CHUB
MACKEREL

TUNA
. SWORDFISH
. EEL
CARP
SUCKER
. BUFFALO
CATFISH
. BULLHEAD
PIKE
PICKEREL
. MUSKELLUNGE
MULLET

. BARRACUDA
. BLUEFISH
POMPANO
BUTTERFISH
. HARVESTFISH
SUNFISH
. BLACK BASS
BASS
. PERCH
. SNAPPER
SCUP
. PORGY

CROAKER
WEAKFISH
. DRUM
FLOUNDER
SOLE
. HALIBUT
. ROSEFISH
CODFISH
SCROD
HADDOCK
HAKE
POLLACK
CUSK

CRUSTACEANS

CRAB
CRAYFISH
LOBSTER
SHRIMP

MOLLUSKS

. ABALONE
MUSSEL
OYSTER
SCALLOP
CLAM
SQUID

PLANTS

CEREALS
WHEAT
FLOUR
PATENT FLOUR
GRAHAM FLOUR
GLUTEN FLOUR
BRAN
WHEAT GERM
RYE
BARLEY
MALT
CORN
CORN MEAL
CORN STARCH
CORN OIL
CORN SUGAR
CORN SYRUP
CERULOSE
DEXTROSE
GLUCOSE
OATS
RICE
WILD RICE
SORGHUM
CANE
CANE SUGAR
MOLASSES
BAMBOO SHOOTS

SPURGE FAMILY
TAPIOCA

ARROWROOT F.
ARROWROOT

ARUM FAMILY
TARO
POI

BUCKWHEAT F.
BUCKWHEAT
RHUBARB
GARDEN SORREL

PEPPER FAMILY
BLACK PEPPER

PINE FAMILY
JUNIPER

MINT FAMILY
MINT
PEPPERMINT
SPEARMINT
HOREHOUND
THYME
SAGE
MARJORAM
SAVORY

LEGUMES
NAVY BEAN
LIMA BEAN
KIDNEY BEAN
STRING BEAN
SOY BEAN
SOY BEAN OIL
LENTIL
BLACK EYED PEA
PEA
PEANUT
PEANUT OIL
JACK BEAN
TONKA BEAN
LICORICE
GUM TRAGACANTH
GUM ACACIA

COCHLIOSPERMUM F.
GUM KARAYA

CALTRAP FAMILY
GUM GUAIAC

SAPODILLO F.
CHICLE

PIGWEED FAMILY
AMARANTH

ASTER FAMILY
LEAF LETTUCE
HEAD LETTUCE
ENDIVE
ESCAROLE
ARTICHOKE
JERUSALEM ARTICHOKE
DANDELION
OYSTER PLANT
CHICORY
CELTUCE
SUNFLOWER SEED OIL

PARSLEY FAMILY
PARSLEY
PARSNIP
CARROT
CELERY
WATER CELERY
CELERIAC
CARAWAY
ANISE
DILL
CORIANDER
FENNEL
ANGELICA
CUMIN

POTATO FAMILY
POTATO
TOMATO
EGGPLANT
RED PEPPER
CAYENNE
CAPSICUM
GREEN PEPPER
CHILI
GROUND CHERRY
TOBACCO

MUSTARD FAMILY
MUSTARD
MUSTARD GREENS
CABBAGE
CAULIFLOWER
BROCCOLI
BR. SPROUTS
TURNIP
RUTABAGA
KALE
COLLARD
KOHLRABI
CELERY CABBAGE
RADISH
HORSERADISH
WATERCRESS
COLZA SHOOTS

LILY FAMILY
ASPARAGUS
ONION
GARLIC
LEEK
CHIVE
SARSAPARILLA

MORNING GLORY F.
SWEET POTATO
YAM

GOOSEFOOT F.
BEET
BEET SUGAR
SPINACH
CHARD
LAMBS QUARTERS

LAUREL FAMILY
AVOCADO
CINNAMON
BAY LEAVES
SASSAFRAS

GINGER FAMILY
GINGER
TUMERIC
CARDAMON

GOURD FAMILY
PUMPKIN
SQUASH
CUCUMBER
CANTALOUPE
MUSKMELON
HONEY DEW
PERSIAN MELON
CASABA
WATERMELON

MADDER FAMILY
COFFEE

TEA FAMILY
TEA

HOLLY FAMILY
MATE

POMEGRANATE F.
POMEGRANATE

EBONY FAMILY
PERSIMMON

PAPAW FAMILY
PAPAW

MAPLE FAMILY
MAPLE SYRUP
MAPLE SUGAR

PAPAYA FAMILY
PAPAYA

MULBERRY F.
MULBERRY
FIG
HOP
BREADFRUIT

IRIS FAMILY
SAFFRON

ORCHID FAMILY
VANILLA

MYRTLE FAMILY
ALLSPICE
CLOVES
PIMENTO
GUAVA

CACTUS FAMILY
PRICKLY PEAR

CAPER FAMILY
CAPERS

RUE FAMILY
ORANGE
GRAPEFRUIT
LEMON
LIME
TANGERINE
KUMQUAT
CITRON

PINEAPPLE F.
PINEAPPLE

BANANA FAMILY
BANANA

ROSE FAMILY
APPLE
CIDER
VINEGAR
APPLE PECTIN
PEAR
QUINCE
. QUINCE SEED
PLUM
PRUNE
CHERRY
PEACH
APRICOT
NECTARINE
. ALMOND
RASPBERRY
BLACKBERRY
LOGANBERRY
YOUNGBERRY
DEWBERRY
STRAWBERRY

HEATH FAMILY
CRANBERRY
HUCKLEBERRY
BLUEBERRY

GOOSEBERRY F.
GOOSEBERRY
CURRANT

HONEYSUCKLE F.
ELDERBERRY

GRAPE FAMILY
GRAPE
RAISIN
CREAM OF TARTAR

OLIVE FAMILY
GREEN OLIVE
RIPE OLIVE
OLIVE OIL

WALNUT FAMILY
ENGLISH WALNUT
BLACK WALNUT
BUTTERNUT
HICKORY NUT
PECAN

CASHEW FAMILY
CASHEW
PISTACHIO
MANGO

STERCULA FAMILY
COCOA
CHOCOLATE
COLA BEANS

MALLOW FAMILY
COTTONSEED OIL
OKRA

PALM FAMILY
COCOANUT
DATE
SAGO
PALM CABBAGE

BRAZIL NUT F.
BRAZIL NUT

OAK FAMILY
CHESTNUT

SESAME FAMILY
SESAME OIL

POPPY FAMILY
POPPY SEED

BIRCH FAMILY
FILBERT
HAZELNUT
OIL OF BIRCH
WINTERGREEN

NUTMEG FAMILY
NUTMEG
MACE

MISCELLANEOUS
HONEY

FUNGI
MUSHROOM
YEAST

The (*) is used to separate subgroups in various biological divisions or families.

Fig. 59.

Rinkel.[13] Before enlarging on this concept, it should be emphasized that the classification of cases of food allergy as to the extent of involvement of the diet is a matter of relative degree. Individual patients vary from those sensitive to a single food to those approaching the ultimate of being complete allergics, a point of view presented in Figure 56. As the therapeutic approach in one extreme is quite different

from that recommended in the other extreme, intermediate cases are handled to the best advantage by avoiding the foods to which the individual is most highly sensitive, by the use of botanically related foods (see Biological Classification of Foods in Figure 59 as modified from Vaughan[14] and Ellis[15]) and those judged to be cumulative offenders in spaced feeding with a sufficient interval between doses to avoid the production of postingestive symptoms. It is well known that sensitivity tends to spread more readily within a given botanical family; this tendency is facilitated by oft-repeated ingestion and diminished by spaced feedings. This knowledge is of particular importance when dealing with such important groups as the cereal grains. It certainly is not in the best interests of the wheat-sensitive patient, for instance, to use corn in unrestricted feedings. In fact, a physician's first responsibility under these circumstances is to determine if corn sensitivity does or does not already exist, and, if not, by all means to instruct the patient in the correct use of this important and closely related food.

The patient with the most advanced food allergy, in respect to the extent of the involvement of the diet, profits by the inclusion in the diet of all available tolerated foods, using each in a single feeding once in three or preferably four days. At this interval of ingestion, a food is not apt to mask itself and if significant sensitivity exists the patient will usually be aware of discomfort immediately following its intake. It is in precisely this fashion that one completes the specific diagnosis in cases of food allergy having a wide base of sensitivity. If some particular food is under particular suspicion and there may be some doubt that it is masking itself when taken at a three day interval (this is quite possible), it should be used for a few times at a five day interval and watched more closely or, preferably, checked by means of an individual food test.

The patient is aided in the task of following a rotating, diversified diet by being furnished a list of foods, such as that in Figure 59, and also with a cross-hatched daily form for a month, listing the interval usage of the permitted foods. Although this type of diet is difficult for the patient to follow, if it is carried out carefully it usually results in eventual improvement. It is true that new sensitivities may be acquired but it is also true that tolerance for avoided foods is usually regained. The net result is definitely on the credit side in respect to both symptomatic relief for the present and the outlook for the future.

Quite obviously, a patient on this type of program will not be able to eat many of the prepared dishes commonly served. These individuals do better by eating simple, primary foods rather than some of the landscaped concoctions of multitudinous foodstuffs so commonly proffered by zealous, oversolicitous hostesses!

One should be warned that not all cases of apparently far advanced food allergy are as hopeless as it might appear at first glance. It com-

monly occurs (i.e., with sufficient frequency to be embarrassing) that when dealing with sensitivity to a food exceedingly difficult to eliminate, such as corn, one will learn suddenly that it has not been completely eliminated owing to the fact that the sources of corn have as yet not been completely catalogued. I recently had the experience of being unable to control chronic, distressing allergic symptoms in a patient with a very wide base of sensitivity in spite of the most careful rotation and diversification of the remaining diet. In spite of repeated observations I was unable to locate any other food which seemed to be producing the typical masked symptoms of which this patient complained. I then learned that corn had not been completely eliminated, that the patient was obtaining sufficient corn starch as an "inert ingredient" in a daily tablet of desiccated thyroid to mask her corn reaction. This fact was learned only as the result of a fortunate lapse of a long week-end without the medication which was followed by an acute reaction immediately after the tablet was again ingested. This patient has been able to take tablets of corn-free desiccated thyroid* without symptoms, and after the complete elimination of corn her rotating, diversified diet is affording complete relief.

SUMMARY

Several misconceptions have distorted the current recognition of food allergy. Contrary to prevalent impressions, food sensitivity is a common cause of symptoms at any age, the history cannot be relied upon to detect sensitivity to specific foods or to rule out that possibility, skin tests with food extracts are not reliable diagnostic procedures and do not constitute an essential part of an allergic investigation, and, lastly, food allergy not only exists to a selected group of foods such as wheat, milk and eggs but may involve any article of the diet and usually does so with an expected incidence in direct proportion to the frequency of ingestion of various foods.

Inasmuch as the very existence of food allergy depends on the demonstration of a cause-and-effect relationship between the ingestion of a specific food and the production or accentuation of allergic symptoms, it follows that diagnostic measures for the detection of specific sensitization should be concerned primarily with observations of the effects produced by the experimental feeding of particular foods. This is best determined by performing individual food tests with several articles of the diet used most frequently and prescribing an initial diagnostic diet as the result of such experimental observations.

In diagnosing a case of food allergy on such a clinical basis one learns the degree of sensitivity that exists to each major food and the extent to which the diet is involved by the sensitization process.

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* A line of common pharmaceuticals available in tablet form excluding corn and other major allergenic excipients is available through the Upjohn Company, Kalamazoo, Michigan, under the trade name "Abergic."

A highly restricted diagnostic diet may be employed with relative safety if the patient has a narrow base of sensitivity; it is contraindicated if the base of sensitivity is wide for such a patient has a tendency to acquire sensitivity readily to any food used in oft-repeated feedings. The treatment in either instance consists of using tolerated foods on a rotating diversified schedule, completely eliminating incriminated foods and using those botanically related on a schedule least apt to be associated with a spread of sensitivity thereto.

The complete elimination of a food is usually associated with a gradually diminishing degree of sensitization which eventually permits its reintroduction into the diet. The exception to this rule is fixed food allergy in which the degree of sensitization is not diminished by prolonged elimination.

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RECENT DEVELOPMENTS IN THE TREATMENT OF ACIDOSIS

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In order to treat disturbances in the acid-base mechanism of the body adequately it is essential that the physiological and biochemical processes instrumental in maintaining a normal balance be thoroughly understood. The discoveries and advances in physiological chemistry in the past several decades have placed the clinical entities of acidosis and alkalosis in the realm of objective medicine and should have removed their treatment from empiricism.

The chemical disturbances manifested in the blood of a patient in acidosis, for example, often give clues as to the basic etiology of the acidosis. However, it is to be emphasized that these disturbances of the acid-base regulatory mechanism are but effects of a primary, underlying disease entity and treatment of the acidosis or alkalosis per se is but a palliative, though essential, procedure in the therapeutic scheme for combating the causative diabetes, pyloric obstruction or whatever else.

REGULATION OF THE ACID-BASE BALANCE

The limits of reaction compatible with life as expressed in terms of pH of the blood are 7.0 and 7.8 which means that the range is on the alkaline side of neutrality but that changes in pH can and do occur without death ensuing. The so-called normal blood reaction is most often quoted as from pH 7.35 to pH 7.45. The mechanisms involved in maintaining this relatively small range in pH in health will be reviewed.

1. **Plasma Buffers.**—These substances exert their buffering action and protect the pH of the blood by producing neutral salts and weak acids or weak acidic salts when reacting with a strong acid or those that react with strong alkalies by producing water and weak alkaline salts. The primary buffer systems of the plasma are represented by the ratios:

$$\frac{H_2CO_3}{BHCO_3}, \qquad \frac{BH_2PO_4}{B_2HPO_4} \qquad \text{and} \qquad \frac{\text{H protein}}{\text{B proteinate}}$$

B represents the monovalent bases, chiefly sodium, H protein the free form and B alkaline proteinate. There is but an insignificant amount of inorganic phosphate in the plasma so that this is of no practical importance. The plasma proteins exert but little buffering action at the pH range of blood and hence are not to be considered

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strong defenders of normal blood reaction. The chief factor concerned in the buffering action of the blood lies in the H_2CO_3:$BHCO_3$ ratio. The hydrogen ion concentration of the blood is equal to the dissociation of H_2CO_3 constant, K, times the H_2CO_3:$BHCO_3$ ratio or $(H^+) = K \frac{H_2CO_3}{BHCO_3}$. The amount of H_2CO_3 present under ordinary conditions is about 3 volumes per cent and $BHCO_3$ about 60 volumes per cent. The ratio, therefore, is $\frac{3}{60}$ or $\frac{1}{20}$, at which ratio the pH is approximately 7.4.

Even though the absolute values of H_2CO_3 and $BHCO_3$ change, if the ratio remains 1:20 the reaction of the blood remains normal.

The bicarbonate system comes into play when excessive metabolic acids enter the body as, for example: $BHCO_3 + HA \rightarrow CO_2 + H_2O + BA$. The $BHCO_3$ is hence lowered and the H_2CO_3 relatively increased; this, however, in health is compensated for by increasing the respiratory rate and exhaling CO_2, thus maintaining the 1:20 ratio. The salt formed (BA) and H_2O are excreted by the kidneys. Alkalies entering the body react with H_2CO_3 as illustrated: $(H_2CO_3 + BOH \rightarrow BHCO_3 + H_2)$. This increases the $BHCO_3$ and decreases the H_2CO_3, hence disturbing the ratio and the Ph. However, excessive $BHCO_3$ is excreted through the urine and in some unexplained manner the H_2CO_3 is also increased, thus, again protecting the reaction of the blood. In the case of excessive H_2CO_3, the respiratory rate is increased thus lowering the H_2CO_3 as well as increasing the $BHCO_3$ from base originating from the red cells.

2. **The Buffering Action of Erythrocytes.**—The role of O_2 and CO_2 transport by the red cells is intimately involved in the buffering action of the blood. Whole blood is a more efficient buffer of excessive acids and alkalies than plasma alone and this is due to a rather complex mechanism involving the erythrocytic carriage of O_2 and CO_2. The accompanying diagram (Fig. 60) helps to illustrate this process.

Carbon dioxide enters the plasma from the tissues because the CO_2 tension is greater in the tissues. Probably only 1 or 2 per cent of the CO_2 is hydrated in the plasma to H_2CO_3, since blood remains in the capillaries for only 1 to 2 seconds and this is insufficient time to form it. The reaction $CO_2 + H_2O \rightarrow H_2CO_3$ is speeded up, however, by an enzymatic catalyst, carbonic anhydrase, present only in the red cells. Most of the CO_2, therefore, must pass into the red cells before H_2CO_3 can be formed or HCO_3 can become available as base.

The H_2CO_3 thus formed in the erythrocyte is buffered by alkali, chiefly K^+, which is made available by the loss of O_2 from oxyhemoglobin. The $KHCO_3$ formed ionizes to K^+ and HCO_3. The latter partly diffuses into the plasma and forms $BHCO_3$, mainly $NaHCO_3$. Because of this bicarbonate shift into the plasma, the ionic equilibrium is

disturbed and $\overline{Cl}$ shifts from the plasma into the red cell. The chloride ion is buffered within the erythrocyte by the K^+ made available by the reduction of oxyhemoglobin.

Some of the CO_2 which enters the red cells combines directly with hemoglobin to form a carbamino compound: $CO_2 + HHb \rightarrow HHbCO_2$.

The above description and preceding diagram specifically apply to the situation at the tissue end of the reaction. At the lung terminal, the processes are reversed and in the diagram the direction of reaction, or arrows, would be reversed.

Of the total CO_2 given off in the lungs, about 92 per cent is directly or indirectly carried or buffered by the red blood cells. Eighteen per

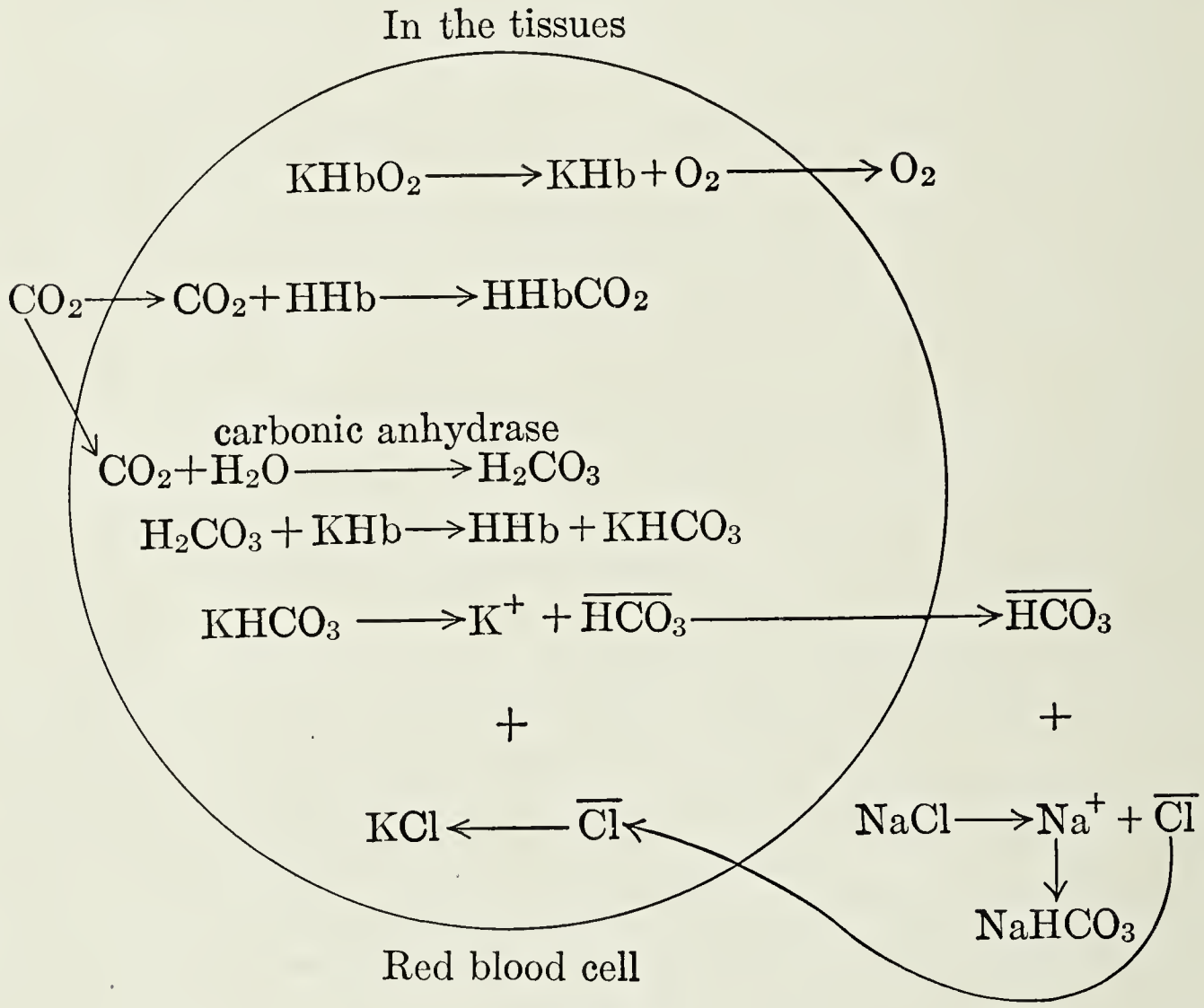
In the tissues
KHbO2 → KHb + O2 → O2
CO2 → CO2 + HHb → HHbCO2
carbonic anhydrase
CO2 + H2O → H2CO3
H2CO3 + KHb → HHb + KHCO3
KHCO3 → K+ + HCO3 → HCO3
+
+
KCl ← Cl
NaCl → Na+ + Cl
NaHCO3
Red blood cell

Fig. 60.

cent is combined with hemoglobin in the form of carbamino compound and 74 per cent comes from bicarbonate—19 per cent as $KHCO_3$ in the erythrocytes and 55 per cent in the plasma as $NaHCO_3$ due to the bicarbonate chloride shift as previously described. The remaining 8 per cent is H_2CO_3 carried by the plasma and formed there without the aid of erythrocytic carbonic anhydrase. In actual transport of CO_2, however, the red cells are responsible for 37 per cent of that liberated in the lungs and the plasma 63 per cent.

3. **The Respiratory Function.**—As mentioned previously, the reaction or pH of the blood is dependent upon the H_2CO_3:$BHCO_3$

ratio. Since the H_2CO_3 content of the blood depends upon the amount of CO_2 that is excreted in the lungs, the respiratory rate is a most important factor in maintaining the acid-base balance of the body. From 800 to 900 gm. of CO_2 are formed and excreted per day by an active normal adult.

4. **Excretion by the Kidneys.**—As important as the lungs in ridding the body of volatile acid, H_2CO_3, is the renal mechanism which excretes the bound or nonvolatile acids and bases, the $BHCO_3$ fraction. The kidneys excrete acids resulting from the metabolism of protein and fat, such as sulfuric, phosphoric and organic acids; these are mainly excreted as salts deriving their base from the tissues or blood. Some weak organic acids, notably β-hydroxybutyric, are excreted per se in the urine. The kidney attempts to conserve base for the body by synthesizing NH_3 from amino acids and excreting the acids or acid salts as ammonium compounds, and reabsorbing the cations, mainly Na^+. The kidney also excretes base when an excess of same is present in the blood; most of this is in the form of HCO_3.

5. **Tests for Determining Changes in Acid-Base Mechanism.**—(a) *Total Carbon Dioxide Content or Carbon Dioxide Combining Power Determination.*—This determination is made by collecting venous blood, protecting it against contact with the air, removing the red cells and saturating the plasma with CO_2 by blowing alveolar air into the liquid. Carbon dioxide is then liberated by the addition of strong acid, is measured and usually expressed as volumes per cent. There are many objections to using this determination as a routine clinical procedure, the chief one being that results are indeed variable. Differences of temperature, exposure to air, time elapsed between drawing of the blood and obtaining the result all add to the variability obtained in the usual clinical laboratory. The most important factor in this variability is the inability to control the bicarbonate-chloride shift between the red cells and the plasma. If a complete air seal is not maintained in the glass syringe and the centrifuge tube, CO_2 will escape from both plasma and red cells. When HCO_3 passes from the erythrocyte (see diagram) $\overline{Cl}$ passes in thus allowing Na^+ available for $NaHCO_3$ formation and falsely increasing the value obtained for the total CO_2 content. Other probably insignificant errors may result in differences in the CO_2 tension of the alveolar air introduced into the centrifuged plasma in different technicians or in the same individual at different physiological times.

If this determination could be relied upon, much diagnostic information would be gained. It would inform of the extent or tendency toward acidosis or alkalosis even before the pH changes; actually, however, compensation is nearly always incomplete and changes in the total CO_2 content of the blood would be correlated with pH changes. As will be discussed later, the metabolic type of acidosis would be associated with a decreased CO_2 combining power while the same

type of alkalosis would be indicated by an increased CO_2 combining power. In the respiratory type of acidosis and alkalosis the reverse relationships would hold. Therefore, it follows that determination of the CO_2 combining power alone without supportive clinical signs or history as to the type of acidosis or alkalosis gives no information whatsoever as to the direction of the change in the blood reaction. Actual determination of the pH of the blood is necessary.

(b) *Blood pH Determination.*—Ideally this measurement should be done on arterial, not venous, blood. However, as will be discussed, venous blood determinations can be made with accuracy. It has been a routine procedure for the past year on my medical service to make blood pH determinations. The ease, the speed and the accuracy of such a procedure speak for its more universal usage. In brief, the method is carried out as follows. A standard Coleman pH meter is used. A sealed glass electrode chamber is fitted with a sterile 2 inch length of rubber tubing, to the end of which is attached a sterile 1 inch needle. To the aspirating side arm of the chamber is attached another 1 inch length of rubber tubing, a thumb clamp and a 2 cc. syringe. The pH meter is standardized prior to each determination with a standard buffer solution of pH 7.4. About 2 cc. of sterile water is drawn into the chamber. The patient's arm is cleansed with alcohol, a tourniquet placed above the elbow and about 1 cc. of blood is drawn from a vein into the vertically-held chamber. The tubing and needle are removed from the chamber and the latter is placed immediately in the meter. The pH is read directly. Readings are obtained in from 10 to 20 seconds after the needle punctures the vein and usually from 20 to 40 seconds after the application of the tourniquet.

Several objections can be made to this method of pH determination among which are (1) venous instead of arterial blood is utilized. Recent work by Grossman* has shown that readings obtained on venous blood are from 0.5 pH to 0.1 pH lower than arterial blood. This is partially compensated, however, by (2) temperature factors. The determinations are made at room temperature and the blood is, of course, at body temperature. This results in values up to about 0.1 pH higher than true readings. The pH range of the blood of normal subjects as determined by Grossman* who utilized temperature correction factors, pressure correction and collected arterial blood under mercury, was 7.35 to 7.60. In contrast, in a series of normal individuals, the range of pH as determined on my medical service using venous blood and employing no temperature correction factors was from 7.35 to 7.45, thus illustrating the dependability of the incorrected venous method.

DISTURBANCES OF THE ACID-BASE BALANCE

For convenience, acidosis and alkalosis are divided into two main types, metabolic and respiratory.

* Grossman, M. G.: Personal communication.

Metabolic disturbances, by far the more common, may be due to other than pure metabolic changes, such as ketosis, and contain elements of disturbances in the regulatory mechanism, such as kidney disease. The disturbance of this type lies in the $BHCO_3$ element of the H_2CO_3: $BHCO_3$ ratio and, as has been noted previously, attempts for defense of the pH are directed toward raising or lowering the H_2CO_3 as the case may be.

In metabolic acidosis the blood pH is lowered beyond the arbitrary limit of 7.35 and the total CO_2 of the plasma would also be decreased beyond the accepted lower limit of 50 volumes per cent. Clinical examples of this type of acidosis include: chronic nephritis, in which there is a retention of nonvolatile acids due to the kidney damage, a decrease in the kidneys' ability to form NH_3 to neutralize acids and the consequent substitution and loss of base from the body; starvation and diabetic ketosis, in which conditions aceto-acetic and β-hydroxybutyric acids are formed in excess, bind base which is lost via the urine; dehydration, in which there is an accumulation of acids that bind base which is lost in the urine; hemorrhage, biliary and pancreatic fistulas cause direct loss of base

Metabolic alkalosis is manifested by an increase of the pH of the blood beyond the arbitrary 7.45 limit. In this type of disturbance the total CO_2 of the plasma would be increased beyond the limit of 75 volumes per cent. Common examples include the alkalosis that occurs in many patients who vomit from pyloric obstruction; acid and Cl are lost, $BHCO_3$ rises and is not excreted through the urine because it is needed to help maintain asmotic pressure. Ingestion of large quantities of alkalies can also cause metabolic alkalosis when the excessive base cannot be excreted adequately by the kidneys.

The respiratory disturbances of the acid-base balance are less common. In contrast to metabolic changes these are under respiratory control and result in changes in the H_2CO_3: $BHCO_3$ ratio. They are compensated by proportional changes in the $BHCO_3$.

The pH of the blood in respiratory acidosis is lowered but, in distinction to metabolic acidosis, the total CO_2 content of the plasma would be normal or elevated—not decreased as in the latter condition. This variance of direction of blood pH and total CO_2 content is due to the mobility of the respiratory mechanism to exhale CO_2 and, hence, it accumulates in the body. Acidosis may occur due to CO_2 excess in such clinical entities as tracheal obstruction, pulmonary emphysema, pneumonia or pulmonary edema.

Alkalosis of respiratory etiology results in an increased blood pH and, in distinction to metabolic alkalosis, a decreased total CO_2 plasma content. Hyperventilation is the common illustration of respiratory alkalosis. This type of reaction disturbance has recently become more important due to the increase in high altitude flying. Hyperventilation does occur at first in altitude but soon ceases; in healthy persons the

effects of altitude hyperventilation are quickly compensated by the usual factors affecting the H_2CO_3: $BHCO_3$ ratio.

Illustrative Cases

1. *Metabolic Acidosis*

This 78 year old white woman was admitted to Wesley Memorial Hospital complaining of periodic, short, numerous attacks of atonic convulsive movements of both hands, arms and shoulders of about one week's duration. Physical examination was essentially negative except for elevation of arterial blood pressure (220/90) and weakness of the right arm and leg. Admission urine showed ++ sugar with no acetone or diacetic acid. Several days after admission the patient suffered a right hemiparesis and became comatosed. Blood sugar rose to 963 mg. per 100 cc. Urine showed + sugar and ++++ diacetic acid. Venous blood pH was 6.92 and CO_2 combining power was reported as 32.5 volumes per cent. The patient expired twelve hours after onset of coma despite insulin, glucose and alkali therapy

2. *Metabolic Alkalosis*

Mr. H. C., a 52 year old white male, entered the hospital for evaluation and treatment of a chronic recurrent duodenal ulcer. His main complaint was early morning epigastric pain. X-ray of the upper gastrointestinal tract revealed a large duodenal crater. Night aspirations of gastric contents showed 50 to 85 cc. of highly acid material (up to 57 units of free acid). He was placed on a strict ventralization regimen consisting of 1.3 gm. (⅓ dram) of sodium bicarbonate and 2.6 gm. (⅔ drams) of calcium carbonate every hour during the day as well as milk-cream mixture. A continuous intragastric drip of milk was instituted for night therapy. On the eighth hospital day the patient complained of nausea, dizziness and a headache. Venous blood pH was 7.78, the urine alkaline. The alkaline powders were withheld, a liter of isotonic saline was given intravenously, and the patient rapidly became asymptomatic. A repeat blood pH done twelve hours later was 7.39. No recurrence was noted.

3. *Respiratory Alkalosis*

This 38 year old white woman was admitted to Wesley Memorial Hospital with otosclerosis for which a fenestration operation was performed. The surgery was done with no particular difficulty and immediately after the operation her condition was satisfactory; she suffered the usual postoperative nystagmus and vertigo. On the first postoperative day, however, she became very excited and her respiratory rate increased to 60 per minute, following which she developed a carpopedal spasm, hyperactive reflexes and tetanic convulsions of the arms and legs following mild stimuli. Blood pH was 7.60. The patient was given reassurance, told not to hyperventilate and given mild sedatives. She became asymptomatic after several minutes and a recurrence was not noted.

TREATMENT OF ACID-BASE DISTURBANCES

It is well to repeat at this point what was stated in the introduction regarding the basic pathology underlying the secondary acidosis or alkalosis. The treatment of reaction changes, though palliative, are essential, indeed at times emergency measures. The diseased kidney, the pyloric obstruction, the diabetes and so forth must be considered the basic therapeutic problem, and the resulting acidosis a temporary complication.

1. **Acidosis.**—As a generality, acidosis of a metabolic nature does exhibit a depletion of $BHCO_3$. The depleted base can be resupplied and should be to the extent warranted by the individual's need. The choice of type of alkali is not a difficult one. In my service we are prone to use isotonic sodium bicarbonate solution if the route be parenteral. This is not available commercially in large quantities so must be prepared. Isotonicity is assured by 0.16 $NNaHCO_3$. Rough calculations as to the amount needed can be made from pH and CO_2 content of the plasma. It is my practice to check this frequently, however, by blood pH determinations during the course of administration.

The question of whether to give alkali to diabetics in acidosis, I believe depends upon the depth of the pH change. In severe acidosis I employ its use but prefer $\frac{1}{6}$ molar sodium lactate in this case rather than isotonic sodium bicarbonate. Because the lactate is metabolized as an added source of glucose is the main reason for its use.

The use of carbon dioxide as a respiratory stimulant in metabolic acidosis is absolutely contraindicated since fatal acidosis ensues. This point cannot be emphasized too strongly since the practice of combining carbon dioxide with oxygen in the treatment of acidosis is not rare. It is important in this regard to recall that the $BHCO_3$ is reduced in metabolic acidosis; to defend the pH the H_2CO_3: $BHCO_3$ ratio must be maintained and certainly this cannot occur if more carbon-dioxide is added to the blood thus separating still further the normal ratio. The use of carbon dioxide-oxygen mixtures as routine procedure in delivery rooms for resuscitating newborn infants certainly cannot be condoned. There is no contraindication to the use of the usual carbon dioxide-oxygen mixtures to increase the depth of respirations following surgical procedures when deep anesthesia has reduced the HCO_3 by blowing off CO_2 and there is a normal amount of base available in the body. But this is the only reaction disturbance in which the use of carbon dioxide is justified.

Ordinarily it is not necessary to give alkali in dehydration acidosis unless it is profound. Sodium chloride does well in this condition.

2. **Alkalosis.**—Metabolic alkalosis, if severe, usually responds quickly and effectively to the use of isotonic salt solution given parenterally. The results are indeed dramatic. Usually patients in alkalosis are nauseated and vomit, which preclude the use of acidifying salts by mouth such as ammonium chloride or calcium chloride.

In profound vomiting the stomach usually ceases to secrete hydrochloric acid and dehydration acidosis often ensues instead of the expected alkalosis so that reaction studies are necessary before treatment can be objective.

Hyperventilation alkalosis if not profound usually becomes compensated shortly after the increased respirations cease. If severe, isotonic sodium chloride given parenterally is indicated.

CHILDREN'S PROBLEMS

Bert I. Beverly, M.D.*

Every child faces many problems in the process of growing up and making a successful adjustment in life. The nature of these problems and the degree of seriousness which they attain are determined by three sets of factors: the child's innate characteristics, the availability of the needs for optimum growth, and the uncontrollable obstacles presented by his environment.

At birth he is not a simple piece of clay capable of being molded into any conceivable shape. Each individual is one infinitesimal unit in the life of all mankind.[1] As such, he is "a living replica of his ancestors for countless generations."[2] He is, therefore, ancient at birth and shaped by the patterns of response which his ancestors formed during the preceding centuries.

THE GROWTH PROCESS

As is the case with every other living thing, man's life is a growth process. It begins with conception and continues to senility. Growth is most rapid before birth but has two other periods of acceleration, infancy and adolescence. It may proceed continuously or be interrupted either before or after birth by injury, toxic or poisonous agents or disease. At times it may even reverse itself as in the deteriorating diseases. An adequate or suitable environment encourages growth after birth, while an unsuitable environment which fails to supply the growth needs may arrest or stunt development or cause regression. This is especially true of emotional growth.

Growth is stimulated by growth energy (vitality). This is a lifetime storage battery with which each individual is endowed at the time of conception. Individuals differ widely in the amount of energy which they possess. Some have it in abundance; the amount they possess is sufficient to them to carry on a vigorous life over a long span of years and to include many activities in addition to the normal routine. Other persons have a limited quantity, sufficient for a shorter life. The force manifests itself in aggression and, under favorable conditions, give rise to constructive behavior. Growth, stimulated by this energy, is the process of unfolding the life patterns which have developed during the millions of years that animal life has existed. Whether we use the term instinct or other words to describe the same phenomenon, we see in life a purposefulness whose ends are

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selfpropagation and self-preservation. These drives are exactly alike in all individuals.

Every child is born with potentialities for the development of those growth patterns which determine his physical stature, intellectual capacity and emotional responses. He also has inherent abilities and handicaps. These vary widely in different individuals. Even persons who have the same degree of general intelligence (I.Q.) show marked differences in such qualities as rote memory, sense of rhythm, mechanical skills, mathematical, spelling and reading abilities. Physical and emotional growth patterns show equal differences. It is obviously impossible to determine all of a child's potentialities at birth but many of them become apparent very early in life. If we are alert to the child's individual qualities and help him fully to develop them (even though they may not be the qualities that we wish he had or think that he ought to have) we will have side-stepped many problems, his mental health can be assured and he can become a competent, well adjusted, happy member of society.

Growth is subject to very little control. Each child uses the equipment with which nature endowed him and grows from within according to the general scheme of human development and to his individual patterns. We cannot increase his size as a builder adds wings to a house; neither can we increase his mental capacity by stuffing him with information or change his personality patterns by persuasion or coercion. In order to have him reach his maximum stature and capacity we can only help him to develop in his own predetermined way. By giving him food and physical care, we help him to achieve his greatest bodily growth. To encourage mental growth we must give him security and supply his intellectual needs. One principle applies alike to the physical, intellectual and emotional aspects of growth: When a child is offered the essentials which he requires for growth he accepts what he needs and develops favorably. The process is complicated and we have only a limited understanding of it, but we know that when his needs are satisfied and no untoward circumstances intervene the child's growth patterns reach their optimum development.

All growth is an orderly process which follows an invariable plan. Embryological studies have shown that the cells which form any given muscle fiber or organ always appear in the same sequence and in the same manner. This is true also of behavior traits. As they unfold in each child we see that they follow patterns common to all humans. Attempts to alter the patterns result in faulty development of the individual. On the other hand, acceptance of nature's plan—that is, a willingness to wait and allow behavior traits to appear at their appointed time—results in the best possible health and development of the child's individual powers, provided, of course, that his growth needs are supplied.

While the order of growth changes is universal, their extent is governed by individual differences and limited by those potentialities which are present in the individual at birth. In this connection, comparisons are not only odious but also dangerous, because no child can be forced to equal or exceed the development of another in order to please an anxious parent. Attempts to hurry him not only do no good but are often harmful.

Like the ultimate limits of his development, the maximum rate of the child's growth is also established and we cannot hasten it appreciably. It varies with the individual and we serve him best by being content to see him grow according to his own pattern without interference. In the case of physical growth we cannot accelerate the process materially by increasing food intake because the quantity which the child desires is determined by his appetite and that, in turn, is an expression of his growth needs. It is futile to force the child to take in more than his body can use.

Again, the same principle applies to mental and emotional growth. A child's learning ability is determined by his capacity for intellectual growth and that is not increased by feeding him overdoses of information. There is a limit to the amount that each individual can grasp at one time; when he is offered more than that amount he is simply incapable of assimilating it. When his intellectual capacity increases it is the result of growth which proceeds from within and not from the urging of too ambitious parents or the offering of too rich intellectual fare. In an analogous manner the youngster accepts the amount of affection which he needs for his emotional growth. Given affection of the right quality and amount, his emotional growth will proceed satisfactorily within his individual limits. They cannot be extended, but if we help the child to reach them we are being far more helpful than if we aim for something beyond his capacity.

Just as children differ greatly in the matter of rate of growth so in any one child different aspects of growth proceed at varying rates. For example, a child whose chronological age is six years may have the physical growth of the average five year old, the intelligence of a child of eight, and the emotional development of one who is four. At school he may show marked differences in his reading, writing, spelling, mathematical, musical and other levels of development. When he reaches adolescence there may be a decided discrepancy between his physiological and emotional growth. It is obvious, therefore, that chronological age is not the proper criterion by which to judge a child. Before accepting any rating as the norm for the particular child it is necessary to recognize that he represents many different age levels. If these different rates of development in the same child are due to inherent growth patterns they cannot be altered. Retardation of certain rates of growth may, however, be the result of unfavorable environmental factors. Differences in the rate of various

aspects of his growth often create problems in the mind of the child. He is troubled and confused when he realizes that he is different from other children, that there is little uniformity in his accomplishments and that he does not conform to the norm arbitrarily set up for him.

Like growth patterns, emotional response (or temperament) appears to be established at birth. Newborn infants exhibit the widest range of reaction to identical stimuli. These reactions may be tested on the examining table by firmly holding the infant's legs, subjecting him to loud noises, causing him to have a sense of falling, or interfering with the nursing process. One infant may be only slightly disturbed, the next may cry mildly, a third may protest vigorously but stop when the insult is discontinued, another may cry violently and continue to do so long after the cause has been removed. These responses to unpleasant situations are constant in each infant. Apparently they continue throughout life, but we do not have sufficient data to establish this point. Pleasant situations also evoke a greater response in one individual than another. These reactions, too, must be accepted; so far as we know they cannot be changed.

Each newborn infant has his individual rhythm of waking and sleeping. Some babies awaken about every two and one-half hours while others can go without attention for longer periods. If each receives food and affection and is made comfortable, that is, if his growth needs are supplied, he will soon go back to sleep. This alternation of sleeping, waking and expressing the need for those essentials which promote growth is apparently in accord with a greater metabolic and physiologic rhythm.

A baby is equipped at birth with several important reflexes which are essential to life. As soon as he is born he automatically begins to breathe. No one needs to teach him to nurse; when his cheek is placed against the mother's breast he reaches for the nipple and sucks. The reflex responses to pain, loud noises, a sense of falling, and restriction of movement are well known. The Moro, or startle reflex, also is present in every normal baby though it is absent when there has been birth injury or other damage to the brain functions.

Another well developed and functioning mechanism with which each infant is equipped at birth causes him to respond to his environment in terms of feeling. This response also is reflex in character. In other words, the baby, like the individual of any age, cannot help feeling the way he does. Because the baby has neither knowledge nor experience he also acts the way he feels. Generally speaking, he responds to his environment either with satisfaction and complacency or with fear and resentment. The former results when his growth needs are satisfied; the latter, when they are withheld or on the occasion of pain, loud noises, a sense of falling and restriction of movement. These responses are the bases of habits. When the former re-

sponse forms a habit pattern it gives rise to self-confidence, the pleasure of achievement and therefore the self-reliance and responsibility which are essential to mental health. There are, of course, justifiable and necessary fears and resentments, emotional responses vital to self-preservation. The fears due to the unfavorable environment as given above, however, create serious problems in the life of the infant.

Even in the case of the infant, life is conflict. He is controlled by primitive drives of self-preservation and propagation and at the same time confronted with a complex and complicated society which is often at variance with his requirements. Being a selfish animal, the infant first demands that his own growth needs be satisfied. As he grows, however, he must learn to conform and by the time he reaches adult life he must curb and sublimate part of his impulses in order to meet the high standards of civilization. This necessity might create a very critical situation if it were not for the fact that adaptability is part and parcel of the growth process. Nevertheless, the twenty or twenty-five year period which our society grants him is a short time in which to reconcile these differences and if the individual is to make a successful adjustment he must have his growth needs supplied in sufficient measure to assure predominance of self-confidence and self-reliance in his personality and to prevent him from being controlled by irrational fears and resentments.

In early infancy the child is passive in his demands; that is, when his needs are not satisfied he merely cries. As he learns to use his body, however, and as intelligence grows and his emotions mature, he tries to gain satisfaction by more active means. His earliest satisfactions result from sucking, elimination, warmth, fondling, and general bodily care. When he becomes more aggressive (as both his demands and his abilities increase) he will become self-confident and successful in satisfying his inner cravings in inverse proportion to the number of obstacles presented by his environment. If the environment holds too many obstacles, that is, if too much is expected of the child, he becomes frightened and resentful and his aggressiveness becomes partly destructive instead of remaining the constructive force needed for successful adjustment. Later, as his conscience awakens and produces in him a sense of guilt, his destructiveness may be turned against himself and cause him to do things which will hinder rather than aid him in his efforts. Menninger[3] says, "If we can imagine a parent sufficiently skillful to replace each satisfaction of which the child is deprived by another satisfaction that the child could accept as approximately equivalent, without disloyalty to the requirements of reality, we should expect to see in the progeny of such a parent an ideal person, not one without aggression but one without a sense of being thwarted in the adventures of life, without hate for anything except those things which should be hated and fought against in defense of his own ideals and best intentions."

At first thought this statement of the growth process seems to be an oversimplification, yet these few principles are the ones which have governed human development through the countless centuries during which the race has been in existence. It is only since the individual has encountered greater difficulty in adjusting to society due to its growing complexity that parents have tried different methods of rearing children and that mental ill health has increased. These different methods, in general, have been attempts on the part of parents to force the growth process. Some of the most common changes in our program for bringing up children have been the imposition of standards too high for infants, forced feeding, too early toilet training and too strict discipline designed to teach children to act like adults. Such excessive demands not only fail to accomplish their purpose but often have a directly opposite effect as the result of thwarting the child and burdening him with problems which make it hard for him to grow up. While it is not possible to reduce the rate or extent of potential physical and mental growth, it is possible to stunt emotional growth and even to cause regression. This is the usual finding in mental ill health.

GROWTH NEEDS

What factors, then, make an environment most favorable for maximum growth?

First, and most important, is *security.* This is the feeling which is given to an infant from the moment of birth by parents who really want him. Not all parents want children; some men and women hate them. These individuals cannot give a child security. This category, however, does not include persons who feel that they should not have children because ill health, overwork or financial difficulties make it impossible for them to give their families sufficient care. The parents who cannot give a child security are those who themselves have not grown up sufficiently to want children or who have deep-seated resentments against them. When they are not wanted by their parents, children, even newborn infants, react with fear and resentment. This is the case even when the parents, suffering from a sense of guilt, try to atone by lavishing affection on the child. He does not consciously know that he is unwanted but when the quality of affection is not normal he fails to derive from it a feeling of satisfaction and complacency.

Complete and unqualified acceptance is the baby's second growth need. Unfortunately, this is not always found even among parents who genuinely want to have children. Because of their own prejudices and anxieties many of them cannot accept the children who are born to them. This may be the case when parents see in a child characteristics which are not there. Frequently, when a child looks like a relative whom the parent dislikes he may visit his resentment on the young-

ster. In any case, the inability of parents to accept a child often prevents normal growth.

The third growth need, which may be considered as a corollary to the second, is the child's need *to grow up according to his own patterns.* As we have seen, no two infants have the same potentialities for physical, intellectual or emotional growth, no two grow at the same rate or reach the same goal. Each child has special abilities and defects and other individual characteristics which, taken as a whole, make up his personality. That being the case, no good purpose is served by trying to hasten growth or any phase of it. If adults keep this fact in mind and approve the child's accomplishments, whatever they may be, he can (provided he has the other environmental opportunities for growth) develop his own abilities to the greatest possible extent. On the other hand, when parents, teachers and other adults attempt to change a child's characteristics, he becomes frightened and frustrated and his emotional growth may, at the least, be restricted.

A *"feeling of usefulness,"* to use Aldrich's expression, is the fourth growth need. Children learn by practice, and the discovery that they can perform various acts gives them self-confidence. They like to do things for themselves and if they are afforded the opportunity will take on responsibilities appropriate to the stage of their development. For example, children from birth take full responsibility for eating a sufficient amount of food; usually they take responsibility for toilet habits during the day at twelve to twenty months, and during the night, by the time they are three years old. Also at the beginning of the third year they usually learn to play with other children and accept the responsibility for settling their differences. All children will take the responsibility for getting to school on time and for doing their work unless the standards are too high for them. Many children, however, are not allowed to take the responsibilities of which they are capable. Adults force them to eat more than they desire, fail to let them feed and dress themselves when they are ready (at about fifteen months and two years of age respectively); and prevent them from playing with other children. Such restrictions, commonly motivated by anxieties and rejection on the part of parents, keep a child infantile and create in his mind unnecessary and often unsolvable problems. This child is usually said to be spoiled, especially when he becomes demanding and has temper tantrums because he has been frustrated.

It is essential also *to apply to a child only those standards of behavior which are appropriate to his age.* This is the fifth growth need. A child requires food, affection and care corresponding to his particular rhythm. This important principle was disregarded a few years ago when strict food schedules were commonly recommended and parents were discouraged from fondling their babies. An infant takes as much food as he needs for physical growth and demands as much

affection as he requires for security. The overdemanding baby is the one who is suffering from physical discomfort or from fear which stems from anxiety on the part of one or more of the persons who are caring for him. In this connection we often hear adults express the popular fear that a baby is being spoiled. Recently, in a hospital, we heard an anxious mother ask why her three week old, sick baby was crying. The graduate nurse to whom the question was directed, answered: "He is spoiled." However, it is not giving attention, but withholding it, which creates difficulties. Failure to give a baby affection of the proper quality when he is emotionally disturbed from any cause creates problems in his mind.

Later, during early childhood and pre-adolescence, many children are again disturbed by parental insistence that they live up to standards which are not appropriate to their age. Usually, these are adult social standards which are above the child's level of intelligence and emotional maturity. Honesty, truthfulness, unselfishness, consideration and other abstract norms cannot be imposed on children. It is impossible for them to be wholly obedient because they cannot possibly do more than a small percentage of the things they are told to do. Nevertheless, parents continue to make excessive demands. They seem to be afraid to be kind to their children, perhaps because they think a show of kindness indicates that they are not behaving as proper adults. This attitude, however, and parental demands that young children observe the rules of conduct accepted by adult society, cause youngsters, even before they are five years of age, to believe that they are bad. A great many of them feel that their parents do not approve of them.

Other problems are created by *lack of proper sex education.* Self-propagation is the strongest force in the growth process. The importance of sex education has been demonstrated scientifically. Nevertheless, "it is also our custom to deny young children an understanding of sex differences, of mating and sex-functioning. They may ask questions and earnestly seek to understand them but we prefer to confuse their young minds and obscure their young minds. Thus when in adolescence they are confronted with puberty and the development of genital functions and all the accompanying alterations of sexual maturation, they are again faced with a sudden and often dramatic reversal of their childhood teachings, notably in the various forms and threats offered as sex education."[4] As a result of the unhealthy attitude of many parents, children are afflicted with frustrations, anxieties and a sense of guilt. These may begin to mount in earliest infancy and create unnecessary problems which make growing up difficult.

THE RESPONSE OF THE CHILD

The problems in a child's mind are revealed by the ease or difficulty he finds in using the tools with which he was born and in gaining

sufficient satisfaction from his activities to make him feel that he can do something well and find a place in society when he grows up. To fit smoothly into our society undoubtedly requires all of a child's innate resources developed to an optimum degree. Nevertheless, nearly all children have sufficient ability to do so provided their growth needs are supplied and the environment outside the home is not too difficult. Unusual difficulties, of course, lie ahead of those who are born with a meager capacity for physical and intellectual development in conjunction with a sensitive nature. They are unlikely to succeed unless they have a sympathetic environment in addition to an unfailing supply of those essentials which they need for growth. The problems of children increase in proportion to the extent to which their growth needs are withheld and obstacles appear in the environment outside the home.

When growing up becomes too difficult children react either by overcompliance or overdefiance. They may become submissive, quiet, obedient, inactive and asocial on the one hand, or, on the other, destructive, disobedient, unruly and overdemanding. While the public generally regards those children who belong to the former group as "good" and those in the latter group as "spoiled," it is important to recognize that they are all exhibiting the reactions of frightened, resentful children whose growth needs have not been provided. Of the two types of children, those who are overcompliant are less likely to become even partially adjusted individuals.

When the environment becomes too difficult, children who have the more serious problems may fail to outgrow their infantile characteristics or slip back to earlier levels of development. For example, they may continue an infantile form of speech, habits of thumbsucking and incontinence, show extreme jealousy of brothers and sisters and persist in playing alone long past the age when they would normally prefer to be with other children. Some of them use enuresis as an expression of resentment, develop tics and compulsive stealing and habits of destructiveness or become bullies; when completely frustrated in talking they may stammer. In the eyes of the average adult these are behavior problems; to the physician or psychologist, they are symptoms of insoluble problems in the minds of the children who manifest them. These symptoms are precipitated by specific frights suffered by a child who is already insecure, frightened and resentful.

SUMMARY

1. Life is a growth process, beginning with conception and ending with senility.

2. Growth is an unfolding of life's patterns, commonly described as instinctive drives.

3. Each individual is one infinitesimal unit in the life of all man-

kind; the newborn infant is a living replica of his ancestors for countless generations.

4. Growth is stimulated by growth energy (vitality) which normally is translated into behavior in terms of constructive agressiveness.

5. Every infant is born with various growth patterns which determine his physical stature, intellectual capacity and emotional response.

6. Growth takes place from within.

7. In all individuals growth of every kind proceeds in an orderly manner according to a specific sequence.

8. The rate and extent of growth vary in different individuals. Neither can be increased but the rate can be retarded and the extent can be limited. This is especially true of emotional growth which can easily be stunted.

9. Just as no two individuals grow at the same rate so the different aspects of growth vary in one individual.

10. Different degrees and different types of emotional responses can be demonstrated at birth. These responses constitute an individual's temperament.

11. Each individual has a characteristic rhythm of sleeping and waking.

12. From the moment of birth infants respond to their environment in terms of feeling. With experience they form habits of responding with satisfaction and complacency or with fear and resentment.

13. An optimum growth is possible if growth needs are supplied.

14. The growth needs, in addition to food and physical care, are: security (produced by being wanted and accepted), the opportunity for a child to grow according to his own patterns, permission to assume responsibilities proportionate to age and ability, standards of behavior appropriate to age and level of growth.

15. The problems in the mind of a child are created by his attempts to grow up and gain satisfaction from feeling that he is useful and important.

16. When growing up becomes too difficult, a child responds in terms of fear, resentment and a sense of guilt. His behavior may take the form of overcompliance or overdefiance.

17. A child fails to reach optimum growth when the process of growing up is beset with excessive difficulty; he may be emotionally stunted or regress to a lower and more comfortable level.

18. Signs of frustration in growth are: Submissive, quiet, obedient, inactive and asocial behavior or destructive, disobedient, unruly and overdemanding behavior. In both cases the behavior is younger than the child's chronological age and represents growth problems in his mind which he cannot solve.

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EPIDEMIC RINGWORM OF THE SCALP

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At the 1946 annual meeting in Cleveland, Ohio, of the American Academy of Dermatology I reported on a survey of the continent of North America concerning the epidemic of ringworm of the scalp and discussed the epidemiology and treatment of the disease.

This survey for the most part was made by reports submitted to me by my colleagues to whom I am much indebted for their cooperation, and to all of whom I extend my thanks.

EPIDEMIOLOGY

The epidemic began in New York and spread westward in an almost direct line. It did not become a public health problem in Boston or in Philadelphia. It was a minor problem in eastern Canada and completely disappeared in western Canada. Except in northern Virginia there was not much activity in the southeastern states. In the southwestern states there were not enough cases to justify the term "epidemic" and most of the cases were due to Microsporon lanosum, the animal microsporon, rather than to Microsporon audouini which was the invading organism in the coast-to-coast epidemic.

From New York City the epidemic took its course through Albany, Syracuse, Rochester, Buffalo, Detroit, and across Michigan into Chicago where there were probably 8000 cases. In the first survey by the Health Department of Chicago the incidence of ringworm of the scalp as determined by examination of the scalp of school children with the Wood filtered quartz light amounted to 2.6 per cent. In the first six months of 1947 the incidence had dropped to 0.9 per cent. Personal reports from individual dermatologists and from directors of public clinics indicate that the epidemic is now rapidly subsiding.

In 1941, Moore of St. Louis stated that he had seen only four cases of Microsporon audouini infection but in 1946 he estimated that there were probably 4000 cases in that city.

In Anderson, Indiana, with a population of 42,000, there were at the peak 438 cases but through the very efficient work of the Commissioner of Health, Dr. Conrad, no new case had been reported in the first six months of 1947.

In Milwaukee there were very few cases and likewise in the state of Wisconsin as a whole. But in St. Paul and Minneapolis there was a real epidemic.

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Kansas City, according to my colleagues, had very few cases and these were not carefully studied.

Going westward the epidemic attracted little attention until the west coast was reached. In the coastal cities many cases were reported but the incidence was not very high.

The causes leading to this epidemic were many and varied. First of all, wartime conditions which prevailed at the time of the epidemic were the most important factors. Small children were transported all over the country to be with their fathers in camps and to see them off at embarkation ports. Hygienic conditions were of necessity poor. Moreover, many mothers of small children were employed in munition factories and were unable to give their children proper care.

It has been stated by many in print that the epidemic was a result chiefly of barber shop contagion, but my observations do not support this view.

First of all the average age of affected children has been found to be between 7 and 8 years. The heads of children of this age come into contact with the seats of all public conveyances and movie theaters. In my own personal observation I have found that the patients averaged two movies a week.

Boys were found to outnumber the girls by 7 to 1 and this fact has been cited in support of the barber shop theory. This can be discounted, however, by the fact that boys wear short hair and never sit still in any seat. The girls found infected usually had pigtails with a part down the back of the head, in which the primary infection usually was found to have occurred.

The location of the principal lesion in my series of cases was found to be on the convex surface of the back of the head which would naturally come into contact with the seats in public conveyances and movies. I have made a point of watching small children in movies sitting down in the front rows slumped in their seats, squirming through double features. Bored to death by some parts of the movies they twist and squirm and deposit, or acquire, as the case may be, any Microsporon audouini which may be current at the time. Clippers are usually used only on the margins of the scalp and rarely on the convex portion of the back of the scalp.

Two photographs (Figs. 61 and 62) are presented in support of the contention that public seat contact has been the most likely factor in the spread of the epidemic of the scalp.

Case I (Fig. 61).—J. S., a boy aged 11, was first seen October 11, 1944. The duration of his infection was undetermined. He had been under treatment for some time with local applications prescribed by the family physician who had given a favorable prognosis. The patient averaged two movies weekly but sometimes attended more as did his associates. Two younger children in the family had escaped infection.

A diagnosis of Microsporon audouini infection of the scalp was determined by means of the Wood filtered quartz light, the microscope and Sabouraud culture.

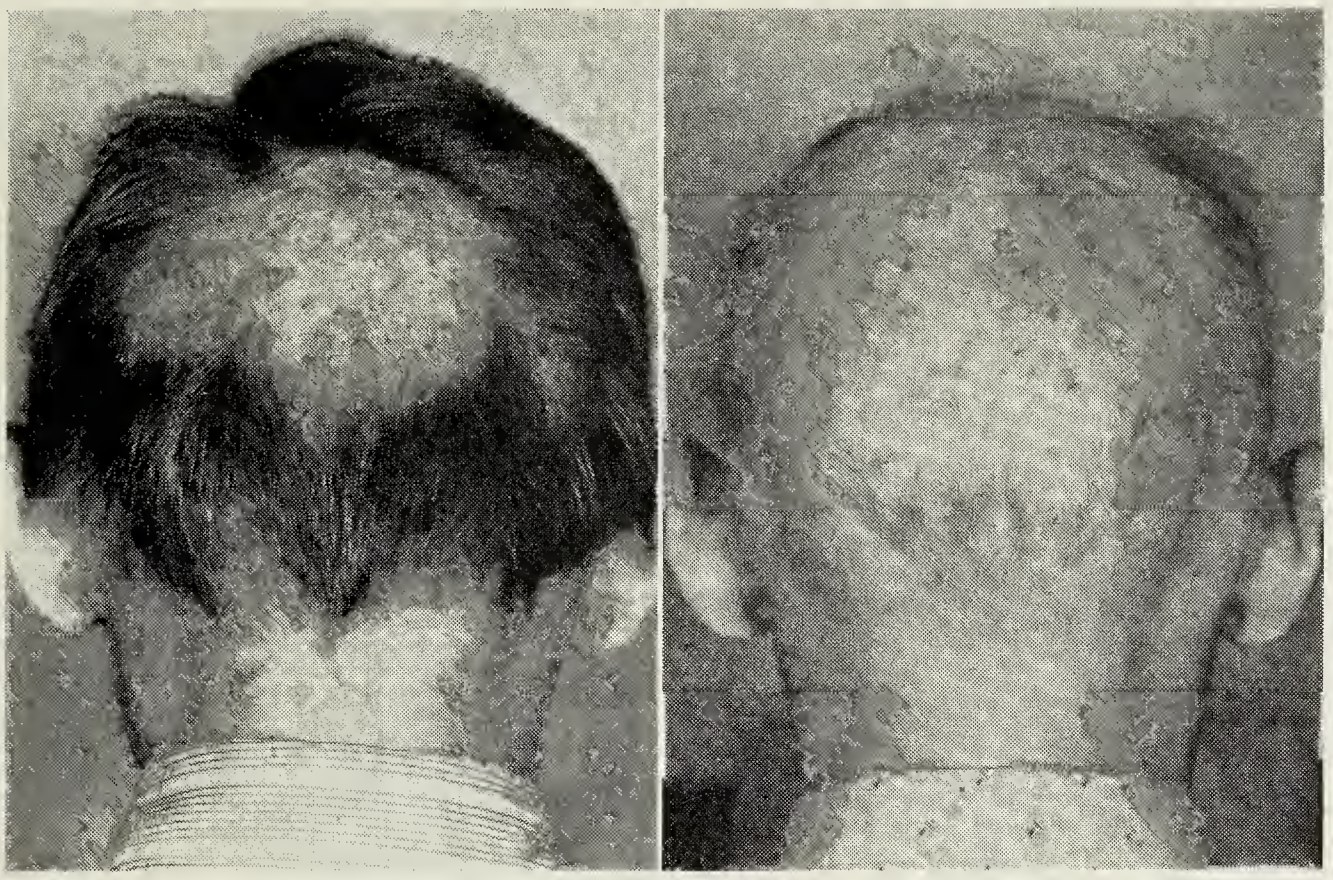

Fig. 61 (Case I).—*Left,* Condition of scalp on first visit. A diagnosis of Microsporon audouini infection of the scalp was made by means of the Wood filtered quartz light, the microscope and the Sabouraud cultures. *Right,* Photograph made November 15, 1944. The epilation appears to be incomplete but the remaining hairs were readily removed by the application of adhesive plaster. When seen January 17, 1945 there was no sign of activity and subsequent examinations were likewise negative.

Fig. 62 (Case II).—Photograph taken before treatment.

The patient was referred to Dr. F. H. Squire, roentgenologist of the Presbyterian Hospital, and an epilating dose of roentgen ray, using the five point technic, was given. A local application of 1 per cent phenylmercuric salicylate in acetone to be applied daily was prescribed.

Case II (Fig. 62).—R. S., aged 9, was first seen February 12, 1945 with a case of short duration. The diagnosis was made by means of the Wood light, microscope and culture tube. Despite the fact that the infection was limited to the back of the head, complete roentgen epilation was advised and given by Dr. Snowden at the Presbyterian Hospital. On March 31, 1945 the epilation was complete and there was no sign of activity. There has been no recurrence.

DIFFERENTIAL DIAGNOSIS OF MICROSPORON AUDOUINI AND M. LANOSUM INFECTIONS

The clinical appearances of ringworm of the scalp due to Microsporon audouini and that due to Microsporon lanosum are usually so much alike that a differentiation cannot be made without examination of the culture.

The audouini infections are considered to be less inflammatory than those of lanosum but the former can produce kerion in rare instances and also produce markedly inflammatory lesions as is shown in Case III (Fig. 63).

Moreover, Microsporon lanosum can produce dry scaly lesions in the scalp without any sign of inflammation as in Case IV (Figs. 64 and 65).

The hairs in both types of infections fluoresce in exactly the same manner and the microscopical appearance of the spores in the hairs in 15 per cent sodium hydroxide preparations is exactly the same.

Examination of the culture on Sabouraud medium and microscopical examination of the culture mounts, however, enables one to make a differentiation of the two organisms with ease and certainty.

Viewed with the Wood filtered quartz light, the so-called "black light," the colony of Microsporon audouini is seen to be brown throughout, whereas the colony of Microsporon lanosum, especially at the edges, is of lavender blue.

Microsporon audouini grows slowly and gradually develops radial grooves with very little tendency towards pleomorphism (Fig. 66).

Microsporon lanosum grows rapidly, becomes fluffy and exuberant and grooves, if present at all, are likely to be concentric rather than radial.

Culture mounts, best made with the glycerine lactophenol fluid, show very definite differences in the two organisms. Microscopically Microsporon audouini will rarely show the presence of spindles or "fuseaux" but spirals or "vrilles" will be found. Microsporon lanosum, however, will present abundance of fuseaux (Fig. 67).

The importance of identification of the fungus lies in the fact that in many instances Microsporon lanosum infections will be found to

respond somewhat more readily to topical applications than those of Microsporon audouini and therefore roentgen epilation may not be necessary.

An outstanding difference in the two types of infections is that the Microsporon audouini infection is strictly a human disease whereas

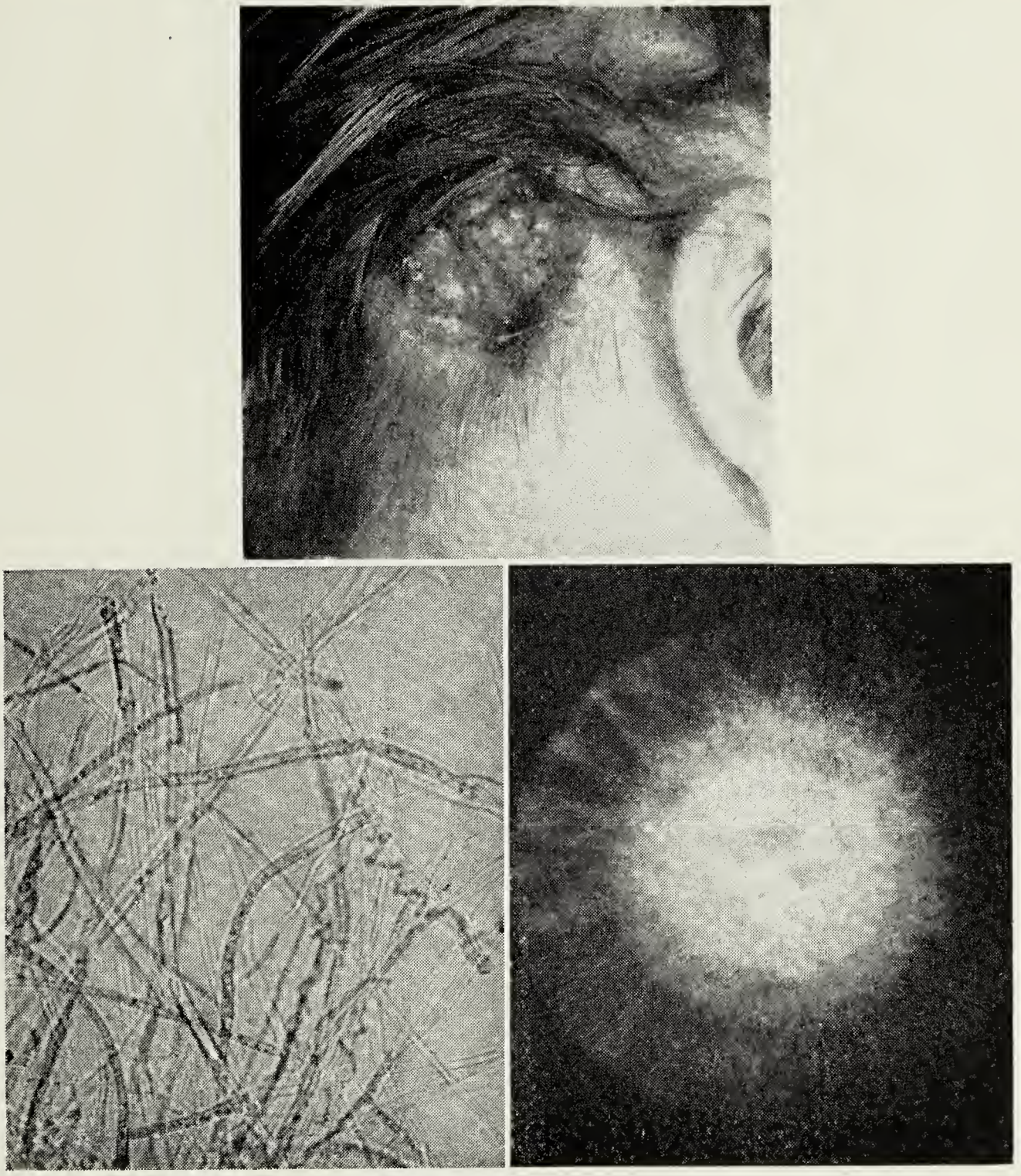

Fig. 63 (Case III).—*Upper,* Microsporon audouini infection of impetiginoid type described by Bloch. When crust was removed there was no kerion beneath. Source of infection undetermined. Female, aged 2½ years. Treatment consisted chiefly of 50 per cent salicylic acid ointment. *Lower,* Gross and microscopic appearance of culture of M. audouini grown from the patient.

infection with Microsporon lanosum can invade with equal ease both humans and domestic animals. I once had the opportunity of seeing six children in as many families with Microsporon lanosum infections acquired from kittens purchased from one and the same pet shop. All of these infections responded to topical applications and none required

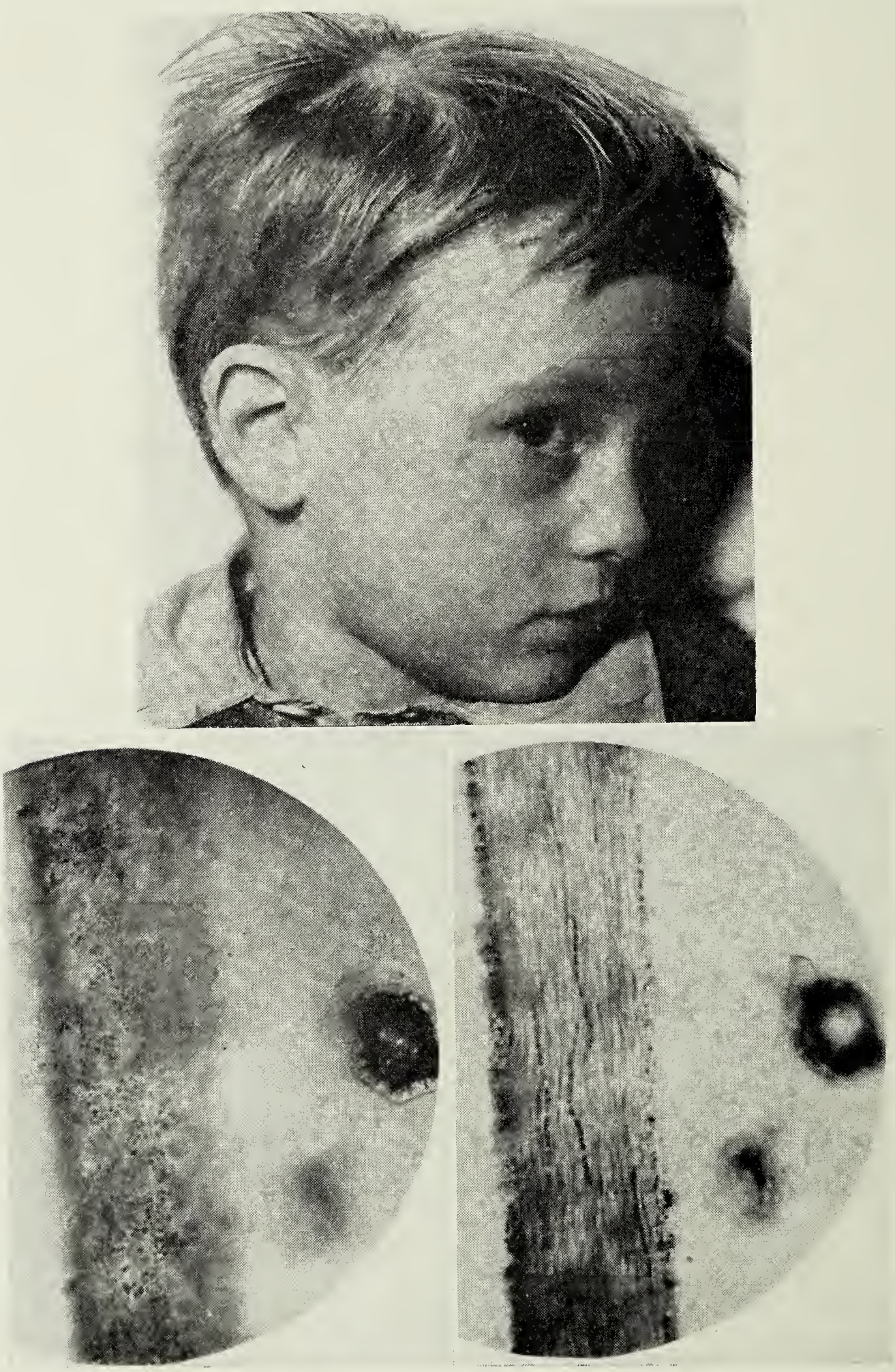

Fig. 64 (Case IV).—*Upper,* Microsporon lanosum infection of scalp and face. Male, aged 3½ years. Duration six weeks. (Arch. Derm. & Syph., 32:166, 1935.) *Lower, left,* Stained hair showing small spores on surface. *Right,* Same field, showing mycelia in shaft of hair.

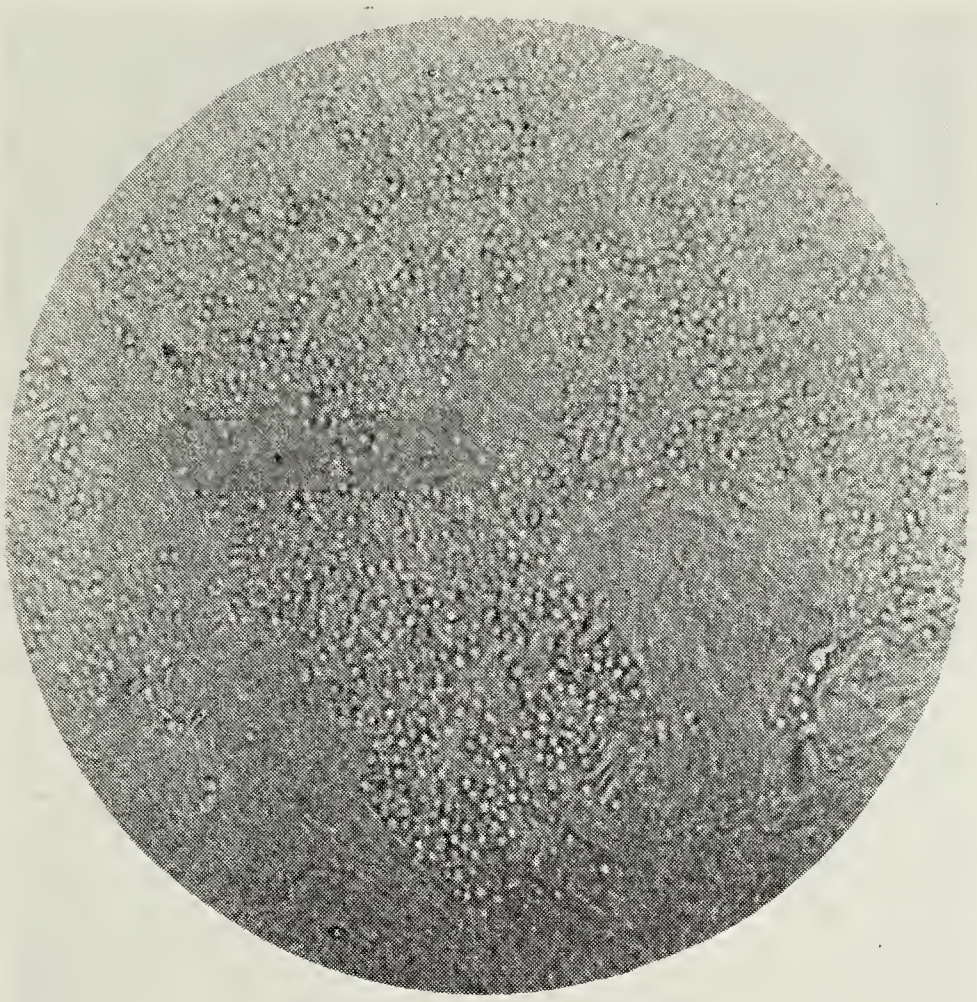

Fig. 65 (Case IV).—*Upper,* Unstained small spores in scales of lesions on face. *Lower,* Showing growth about hair 48 hours after planting on agar.

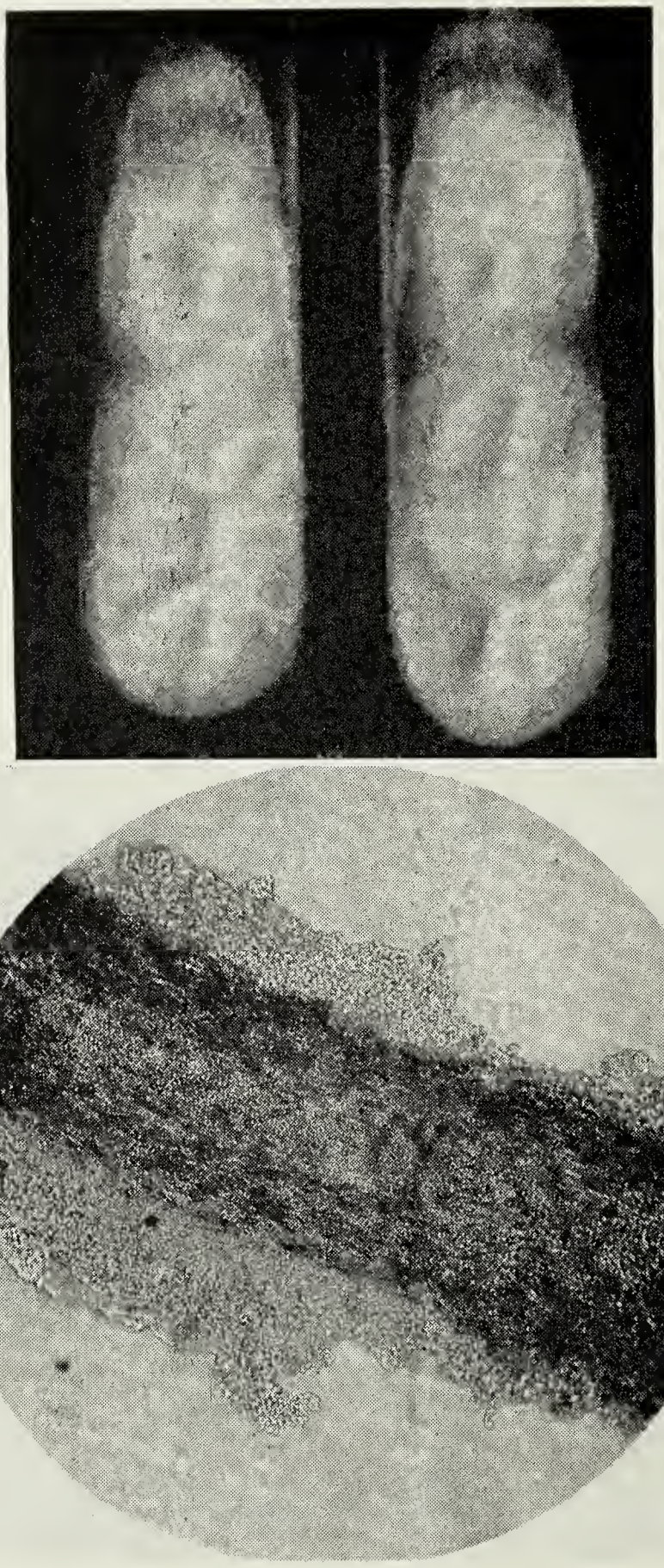

Fig. 66.—Microsporon audouini infection. *Upper,* Cultures from the scalp of two Negro children. The radiating depressions are characteristic. Parasitic for humans only. *Lower,* Infected hairs from one of above Negro children. The shaft is entirely surrounded by mosaic of small spores.

Fig. 67.—Culture mounts, best made with the glycerine lactophenol fluid, show very definite differences in the two organisms. Microscopically Microsporon audouini will rarely show the presence of spindles or "fuseaux" but spirals or "vrilles" will be found. Microsporon lanosum, however, will present abundance of fuseaux.

roentgen ray epilation, which fits in with what was said above as regards differentiation in the treatment of the infections of the two organisms.

An interesting fact concerning the Microsporon audouini infection is that the infection usually clears spontaneously at puberty. In the thousands of cases found in the survey of the Chicago public schools, the oldest patient was a boy of 14 years. A good example of the spontaneous healing of the infection is shown in Case V.

Case V.—P. Z., aged 15, was first seen February 1, 1945, with an infection of several years' duration. Microsporon audouini was proved as the causative organism by means of the Wood light, the microscope and culture. The mother of the

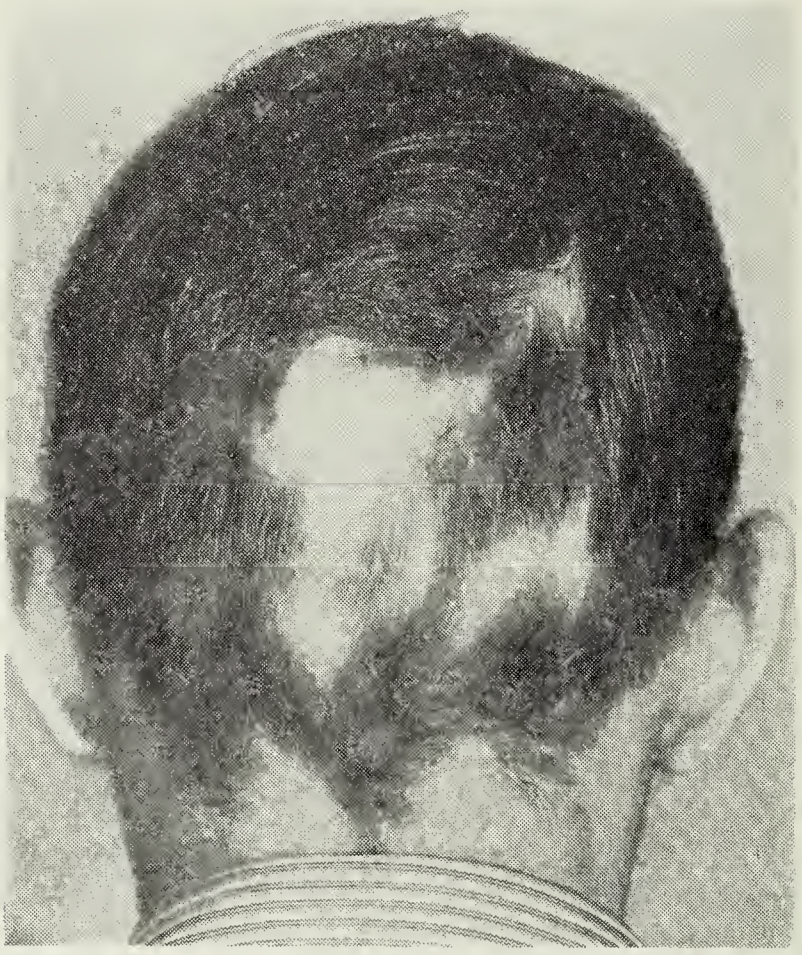

Fig. 68 (Case V).—The condition present at the first examination. There were only a few areas of activity at the margins of the bald spots.

patient had been diligently epilating the infected hairs for some time. On the occasion of the first examination there were only a few areas of activity at the margins of the bald spots (Fig. 68). Because of the age of the patient a topical application was prescribed and the mother was advised to continue manual epilation and to return the son for examination. When last seen two months later there was no sign of activity.

Mothers of children were uniformly concerned about infections in their scalps and a routine examination was made by way of reassurance. A very large percentage of mothers were examined, of whom only one was found infected. This patient was a woman, aged 33, who had a daughter, 6 years of age, with typical Microsporon audouini

infection of the scalp. The mother presented an area the size of a silver dollar above the right ear. The organism was identified on Sabouraud's medium (Fig. 69). The only other case of Microsporon audouini infection in the scalp of an adult I have seen was presented by Drs. I. M. Felsher and Clark M. Finnerud at the meeting of the Chicago

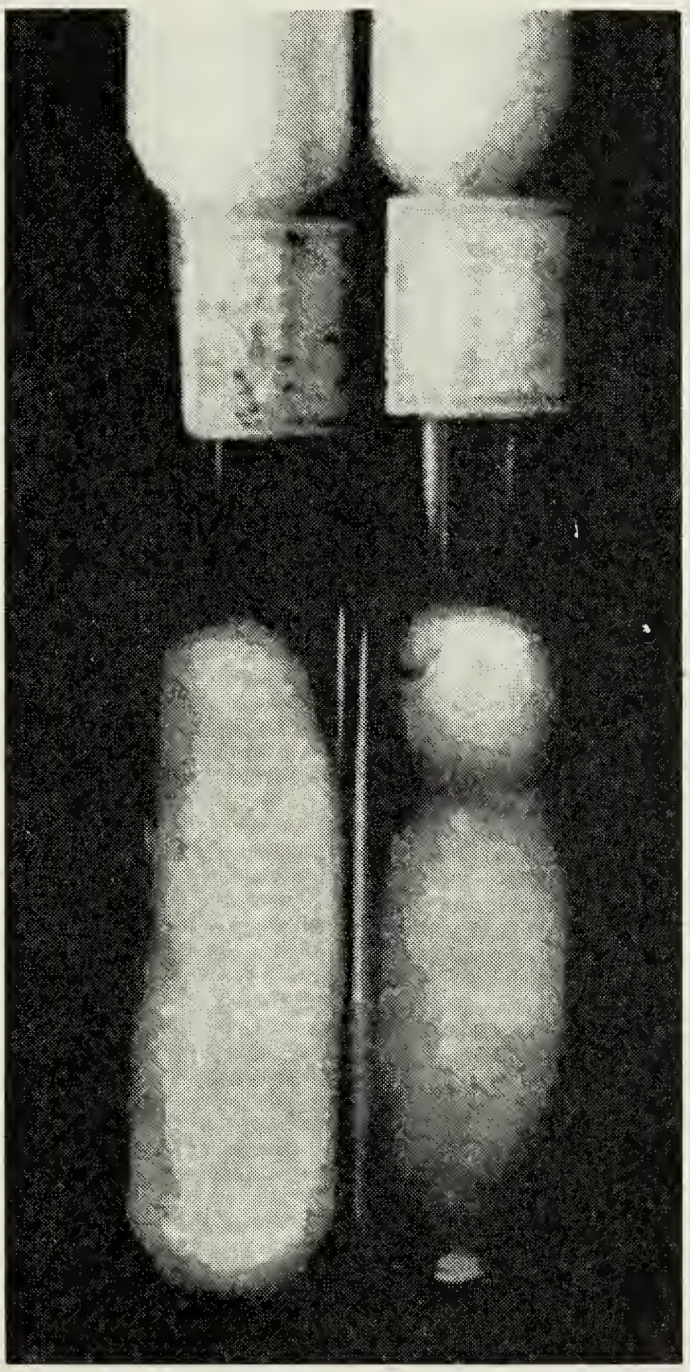

Fig. 69 (Case VI).—Microsporon audouini infection of scalp of child and of glabrous skin of mother. Boy, aged 6, was seen in April, 1934 with typical areas in scalp. The microscopic and cultural findings were typical of M. audouini. Six weeks later the mother called attention to a dime-sized area on the posterior left shoulder. The culture of this lesion is seen above on the left and that of the scalp of the son on the right.

Dermatological Society, October 16, 1946. In their case the infection was much more extensive.

Infections of the scalp or of the glabrous skin of an adult is so rare that any such case merits attention. Case VI (Fig. 69) is the only example of infection of the glabrous skin of an adult which has come under my observation.

TREATMENT

Topical Applications.—Treatment of Microsporon audouini infections of the scalp with topical applications has been disappointing and was abandoned by Sabouraud in the 90's in favor of roentgen ray depilation. At that time schools were established for the children in Paris and they were kept in the schools until cures were certain.

At the beginning of the epidemic in Chicago I tried all of the time-honored applications with very little success and eventually resorted to roentgen ray depilation as a routine treatment. Since the peak of the epidemic has been reached and the epidemic is definitely on the decline it may be that external application will be found to be of more value. Wartime conditions have ceased to exist and children are certain to be given more attention and care.

Among the many applications used and probably as effective as any was 10 per cent of iodine crystals in goose grease. During the war, goose grease was difficult to obtain. Mr. Hutton, pharmacist at the Presbyterian Hospital, supplied the grease from his own geese. The mixture of the crystals of iodine and goose grease should be heated for at least thirty minutes in a double boiler before the iodine will go into solution.

Another preparation used consisted of chrysarobin in 5 to 10 per cent strength in traumaticin, which is a former N.F. preparation known as liquor guttae perchae.

Whitfield's ointment with the following formula was used in full and half-strength. This consisted of salicylic acid 2 parts, benzoic acid 4 parts, and unguentum petrolatum to make 30 parts.

Ammoniated mercury ointment in 5 to 10 per cent strengths was used in many cases but patch testing should always precede the use of this ointment because of the high percentage of sensitized individuals found on routine patch testing. The value of the ointment as a fungicide is practically nil but it does keep down purulent infections and also prevents the floating about of loosened infected hairs.

In one of the many wartime efforts in which I participated, a search was made for a fungicide that would be effective in the Navy under tropical conditions to prevent interference from fungi with radio communications. The most effective fungicide found was phenylmercuric salicylate. This, however, is highly toxic and must be used with great care. One per cent solution in acetone of this chemical was found to be effective in many cases of ringworm of the scalp but had to be abandoned in some cases because of the irritation of the skin.

The most publicized topical application was that using 5 per cent salicylanilide in Du Pont's carbowax, as carried out by Schwartz and his co-workers of the United States Public Health Service in a public school in Maryland. The claim made that 100 per cent of cures resulted would seem in the light of my personal experience with this preparation a bit, to say the least, roseate. Of the many carbowaxes,

No. 1500 should be used. The mother should be instructed to use plain water, without soap, when washing the scalp after the application of the ointment inasmuch as soap makes a gummy mixture which is not easily removed.

So many preparations for the treatment of ringworm of the skin and scalp are described and widely advertised that it was thought advisable to make a crude test of the fungicidal and the fungistatic effects of these preparations.

Hairs taken from the patch in the posterior portion of the scalp in Case II were planted on Sabouraud's medium after covering the hairs with the preparations in the following order: (1) control, (2) "Safety-Soap," (3) equal parts of phenol and camphor, (4) phenol and camphor with the addition of water, (5) Zephiran Chloride, (6–7) Sopranol ointment, (8) 1 per cent phenylmercuric salicylate.

All of the inoculations grew luxuriantly with the exception of those made with phenylmercuric salicylate. With that chemical there was no growth of any kind..

It may be recalled that De Kruiff, the Reader's Digest expert on all medical matters, resurrected an ancient article by a retired army surgeon on the treatment of athlete's foot with a mixture of equal parts of phenol and camphor. This mixture is inert and a nonelectrolyte until water is added, when the phenol is liberated, the presence of which can be readily determined by the addition of ferric chloride. The dermatitis which resulted from the advocacy of the use of this mixture kept the dermatologists busy treating phenol burns for the following year.

This mixture was independently described by an Italian physician and a French physician in the 1840's. Later it was commercialized as Camphophenique and put on the market by a St. Louis company. So many cases of dermatitis resulted that it was given a full page report of investigation by Dr. Puckner in the *Journal of the American Medical Association* (Vol. 48, p. 1364, 1907). As a result of this report the proportions were subsequently reduced to 20 per cent phenol and 30 per cent camphor with 50 per cent mineral oil.

Another widely advertised preparation known as Desenex was tested by covering the hairs with the ointment and planting them on Sabouraud agar. No attempt was made to remove the ointment from the hairs before planting. It was found that Microsporon audouini infected hairs coated with Desenex ointment will bring forth luxurious colonies of Microsporon audouini as if no such ointment had been applied. Mixing equal parts of a culture of Monilia albicans and Desenex ointment delays the growth only slightly.

Roentgen-Ray Depilation.—The most effective and time-saving and therefore the most desirable treatment in an epidemic of Microsporon audouini infection of the scalp is depilation by the means of the roentgen ray. Under the supervision of Dr. F. H. Squire, radiologist of the Presbyterian Hospital, hundreds of patients were depilated in the hospital and in my office by Mrs. Pauline Campbell, who was trained by Dr. Squire. Using the five-point technic and a depilating dose of 350 r to each point, excellent results have been obtained without any untoward sequelae.

That there is a wide margin of safety is shown by the fact that one boy was given, according to the written statement submitted by the radiologist of one of our smaller hospitals, 1250 r to two large "spot" depilations on the right side of the back of the scalp. More than a year was required for a regrowth of the hair but at present although the hair is slightly thinned it is not noticeably so.

* J.A.M.A., *48*:1364, 1907.

"Spot" depilation has been advised by Dr. George Lewis and others but after a few trials I have discontinued such depilation inasmuch as I have found that, after depilating the spot, activity has developed around the depilated areas.

After a depilating dose of roentgen ray the difluvium is practically complete in four weeks at which time the patient is asked to return for observation. If there are scattered hairs remaining they are removed by applying adhesive plaster over the areas in which the stubs of hairs remain. By this technic the scalp can be completely depilated and the patient is advised to continue one of the various ointments for another month at which time there should be an examination with the Wood light.

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